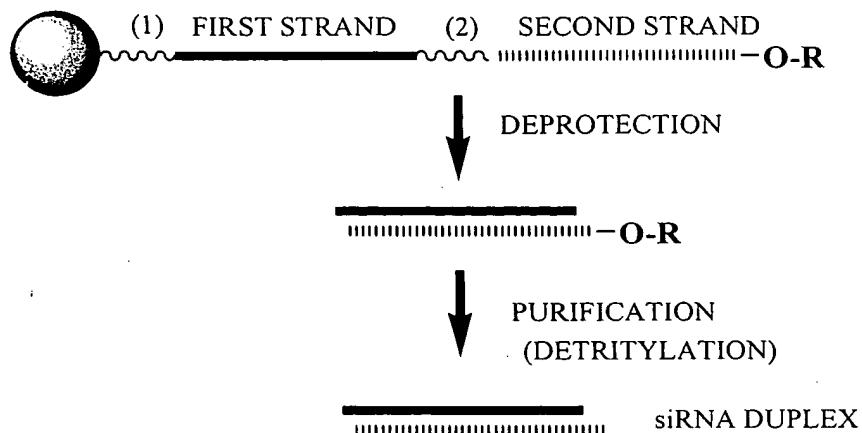


Figure 1

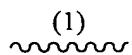


= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP

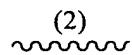
FOR EXAMPLE:

DIMETHOXYSYTRITYL (DMT)



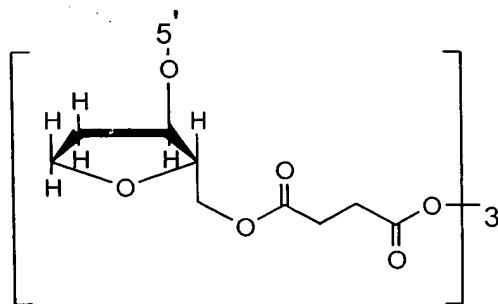
= CLEAVABLE LINKER

(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR
INVERTED DEOXYABASIC SUCCINATE)

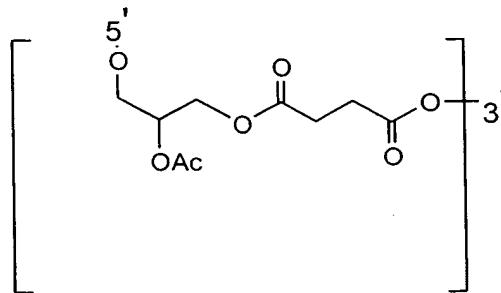


= CLEAVABLE LINKER

(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR
INVERTED DEOXYABASIC SUCCINATE)



INVERTED DEOXYABASIC SUCCINATE
LINKAGE



GLYCERYL SUCCINATE LINKAGE

Figure 2

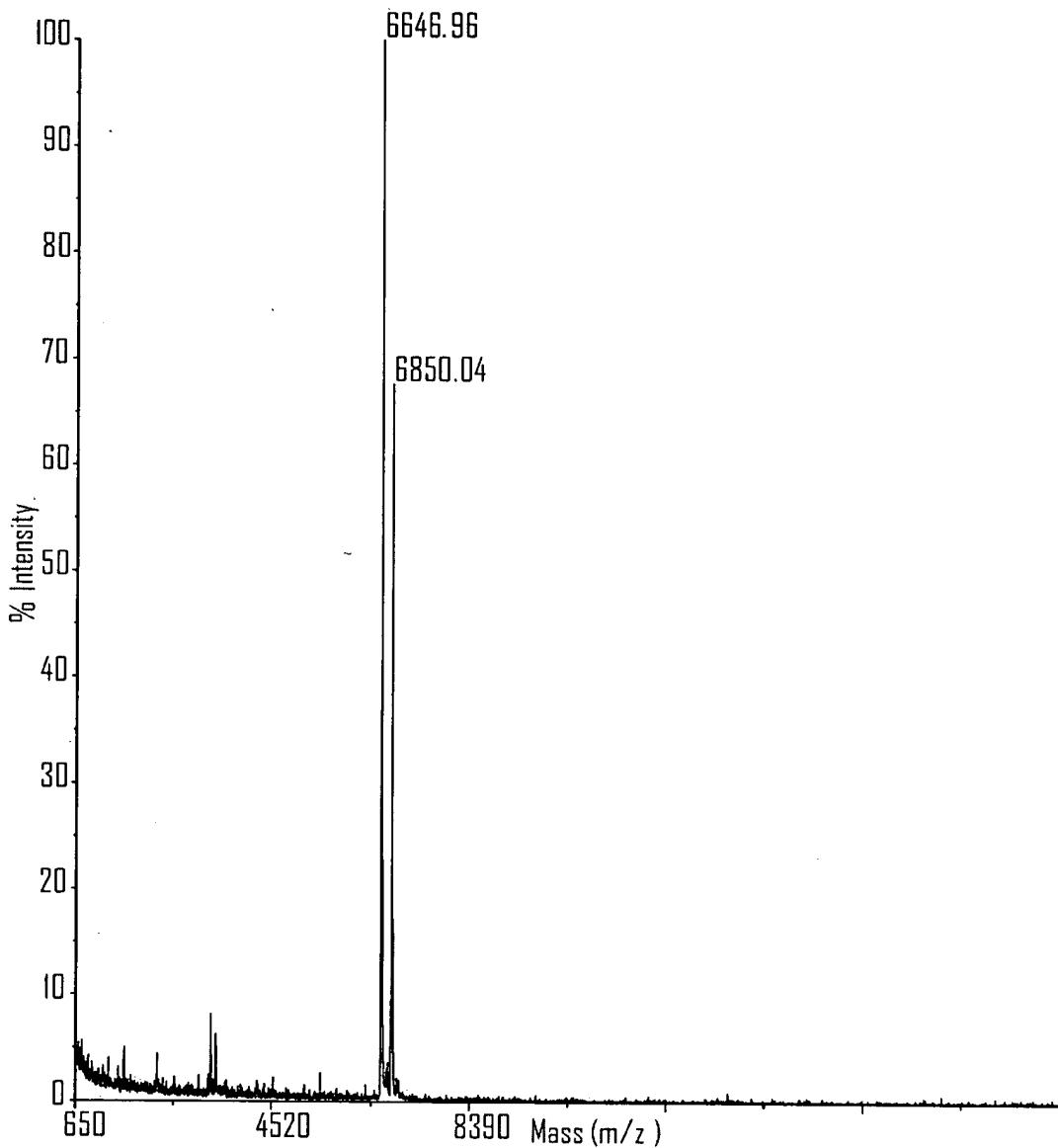


Figure 3

5'-CGUACGGGAAUACUUUCGATT (SEQ ID NO: 394) $T_{1/2} = 15 \text{ seconds (control)}$
 3'-TTGCAUGCGCCUUAGAGCU (SEQ ID NO: 395)

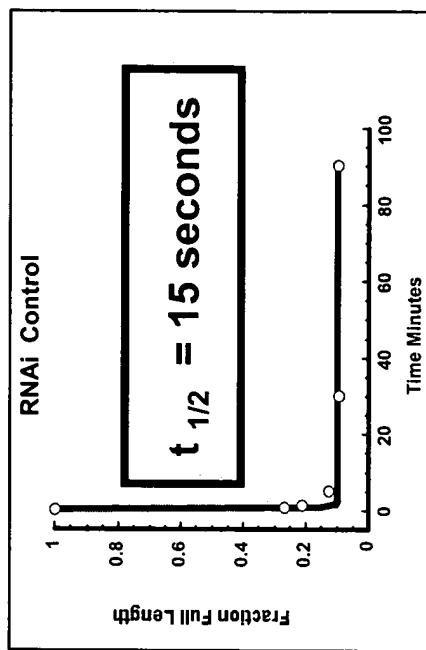
 5'-B cAACCAAAuAcAACATT B (SEQ ID NO: 396) $T_{1/2} = 138 \text{ min}$
 3'-TXGuuGGuGuuuAuGuuGuu (SEQ ID NO: 397)

 5'-B cAACcAcAAAAuAcAACATT B (SEQ ID NO: 396) $T_{1/2} = 3.7 \text{ days}$
 3'-TDGuuGGuGuuuAuGuuGuu (SEQ ID NO: 398)

 5'-B cAACcAcAAAAuAcAACATT B (SEQ ID NO: 396) $T_{1/2} = 72 \text{ minutes}$
 3'-XTGuuGGuGuuuAuGuuGuu (SEQ ID NO: 399)

 5'-B cAACcAcAAAAuAcAACATT B (SEQ ID NO: 396) $T_{1/2} = 40 \text{ days}$
 3'-LTGuuGGuGuuuAuGuuGuu (SEQ ID NO: 400)

 5'-B cAACcAcAAAAuAcAACATT B (SEQ ID NO: 396) $T_{1/2} = 32 \text{ days}$
 3'-tTGuuGGuGuuuAuGuuGuu (SEQ ID NO: 401)



G, A, U, C = Guanosine, Adenosine, Uridine, Cytidine
 T = Thymidine
 Lower Case = 2'-deoxy-2'-fluoro
 S = phosphorothioate
 B = inverted deoxyabasic
 D = inverted Thymidine
 X = 3'-deoxy Thymidine
 t = L-thymidine
 L = Glyceryl moiety

Figure 4

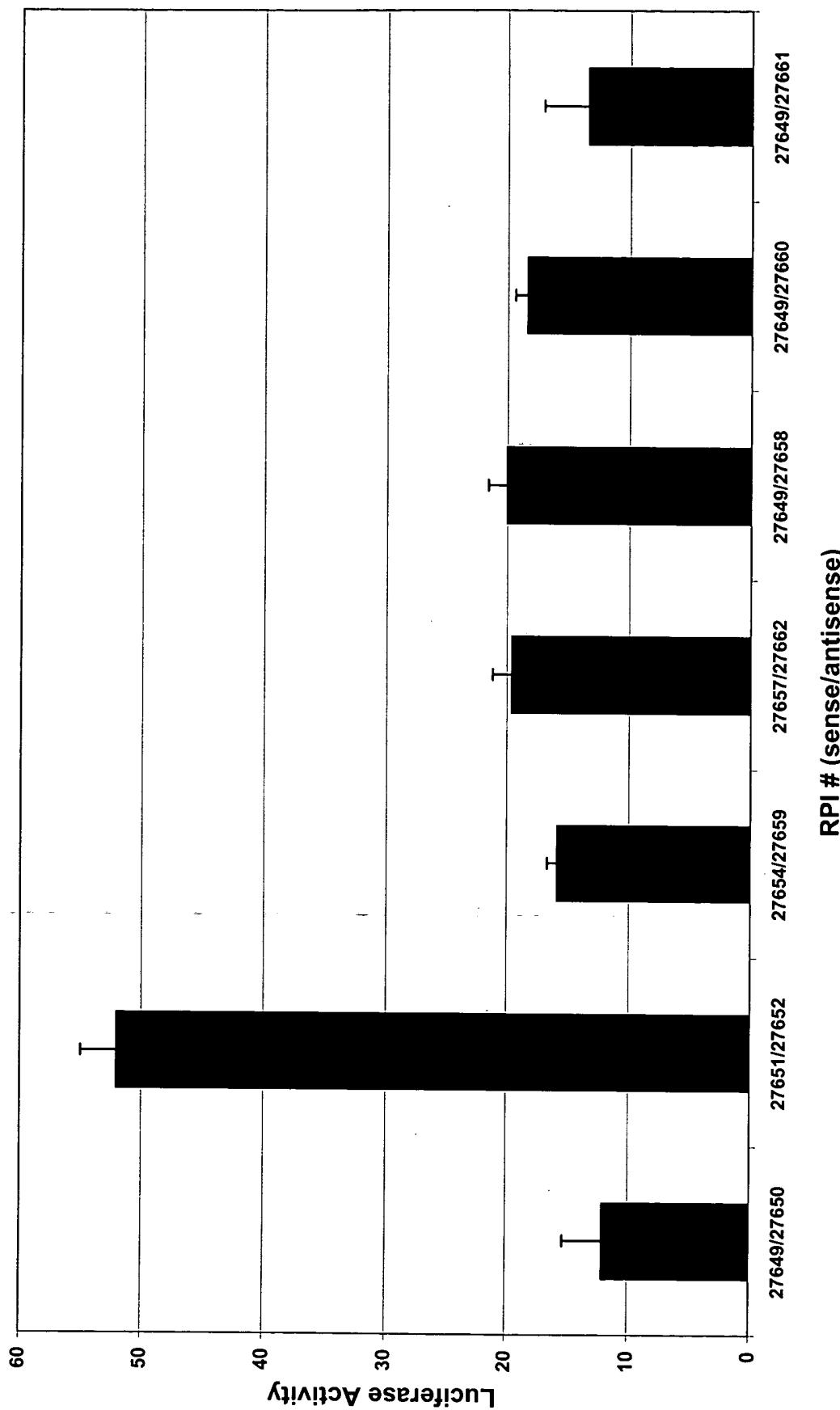


Figure 5

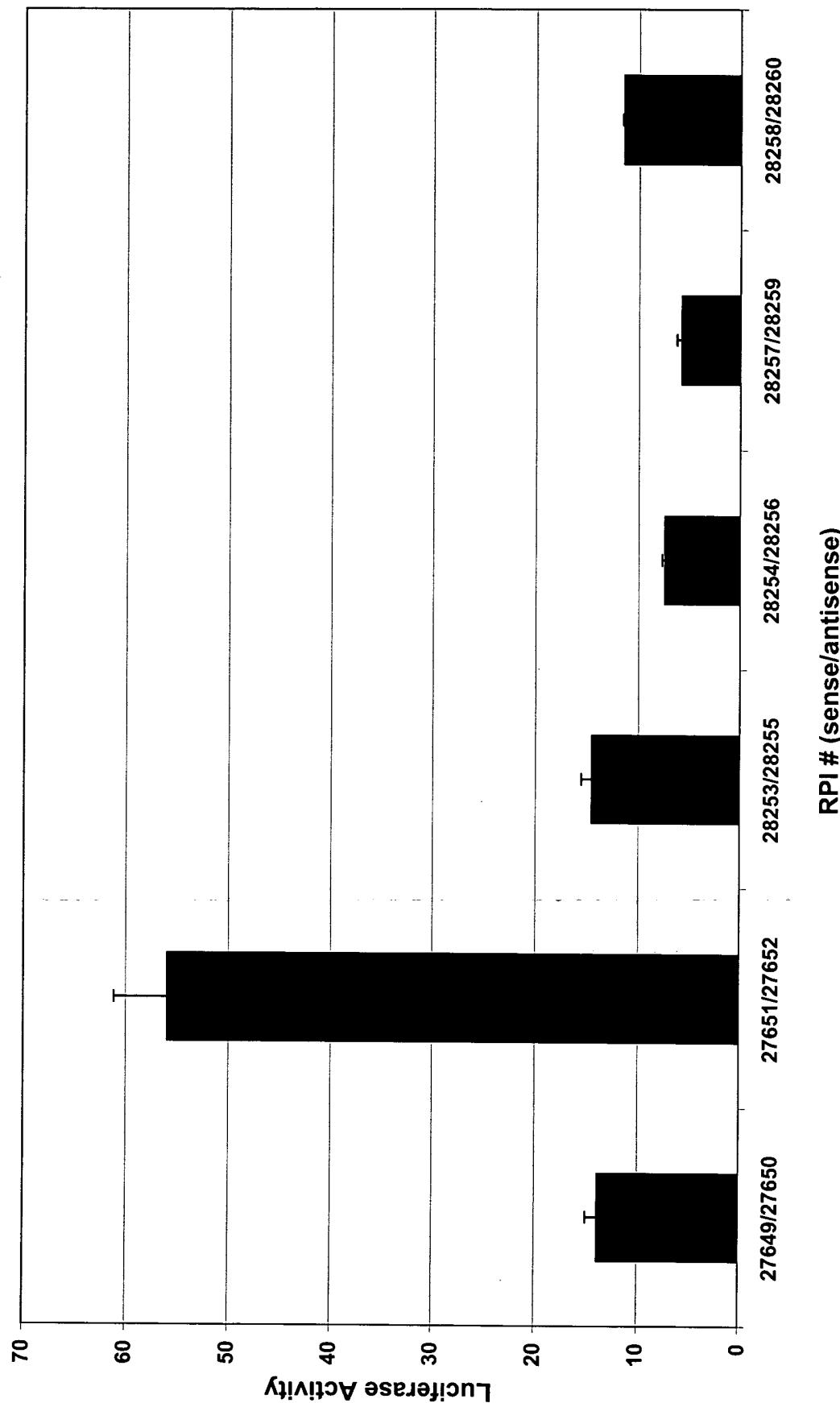


Figure 6

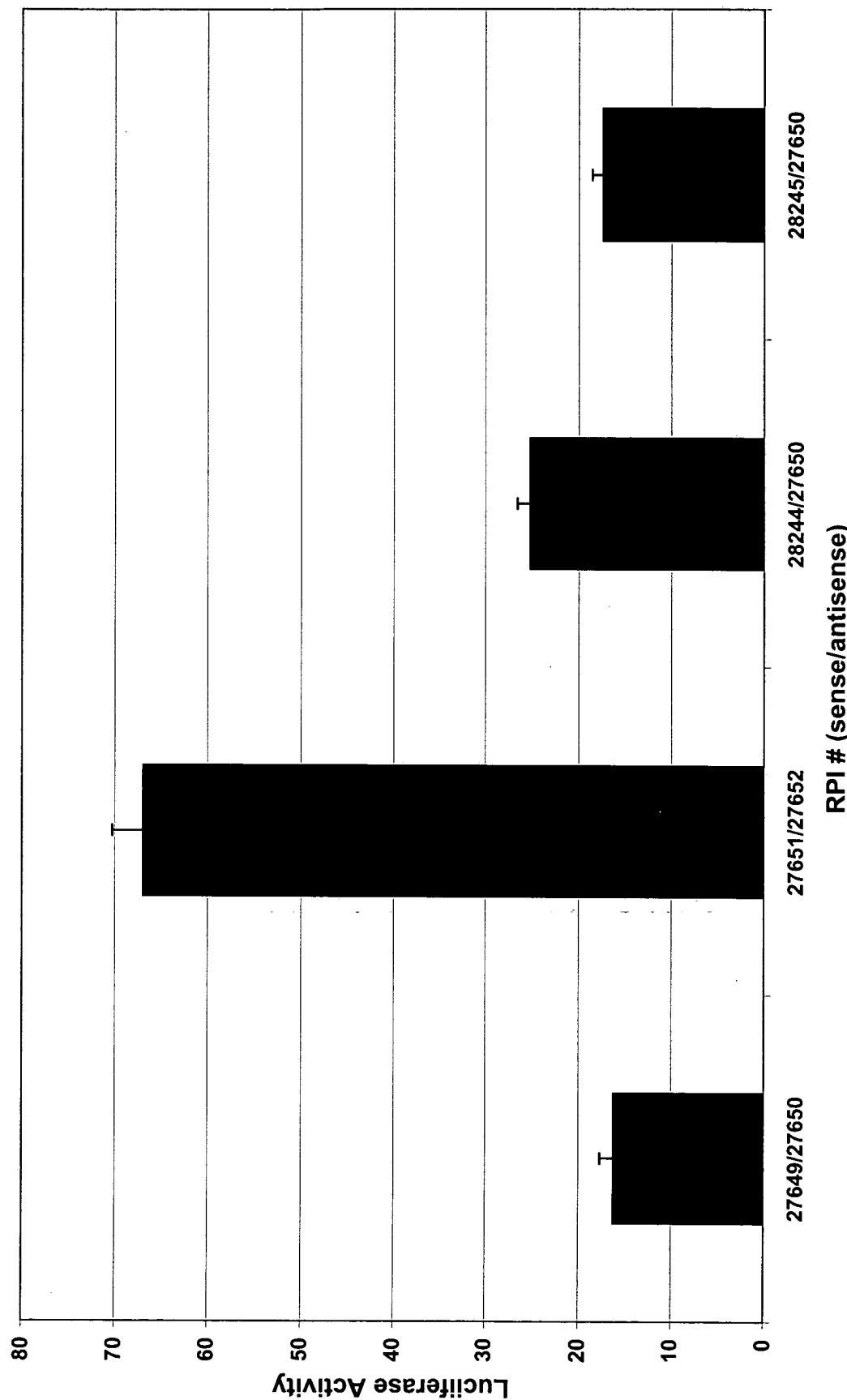


Figure 7

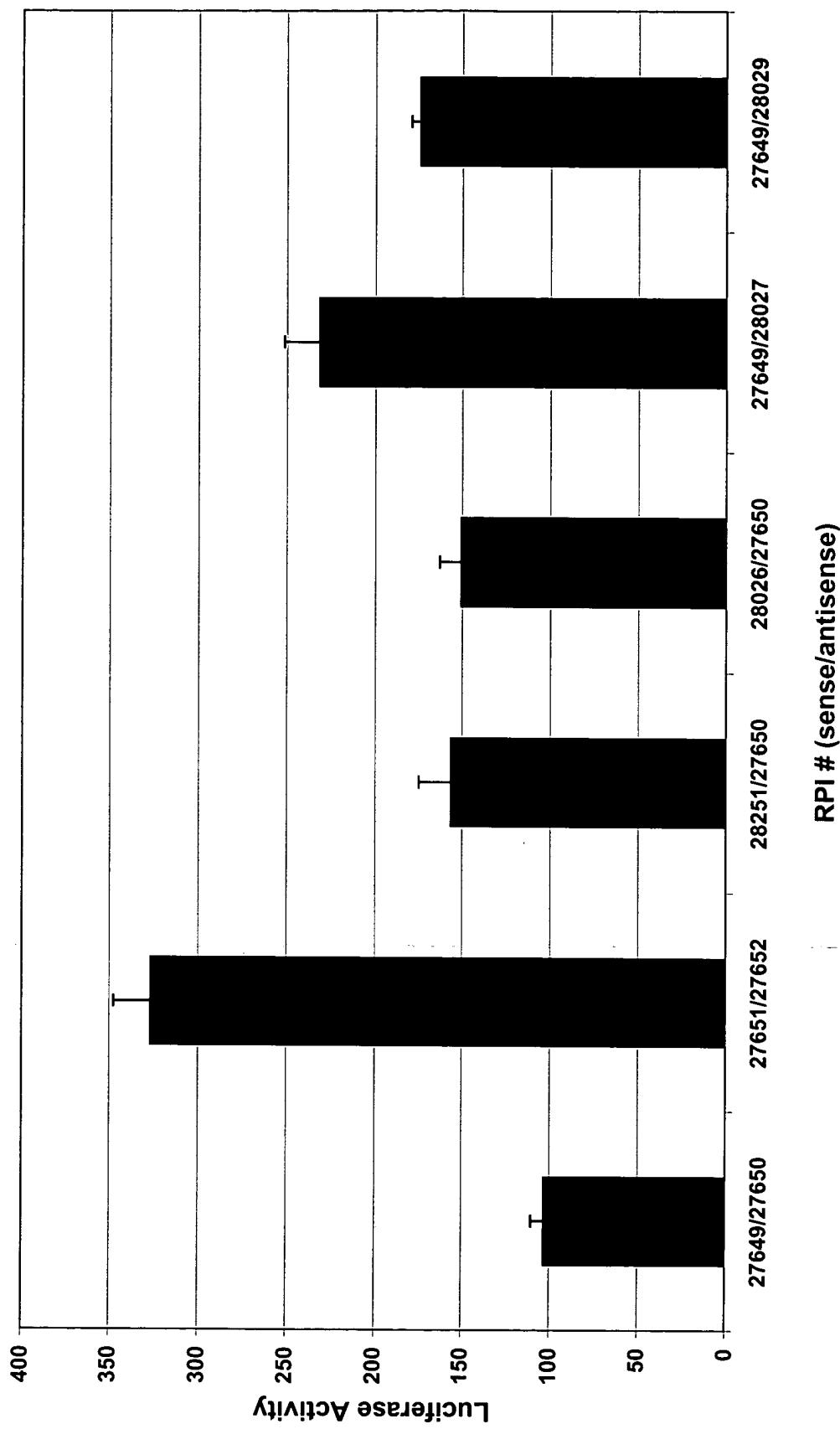


Figure 8

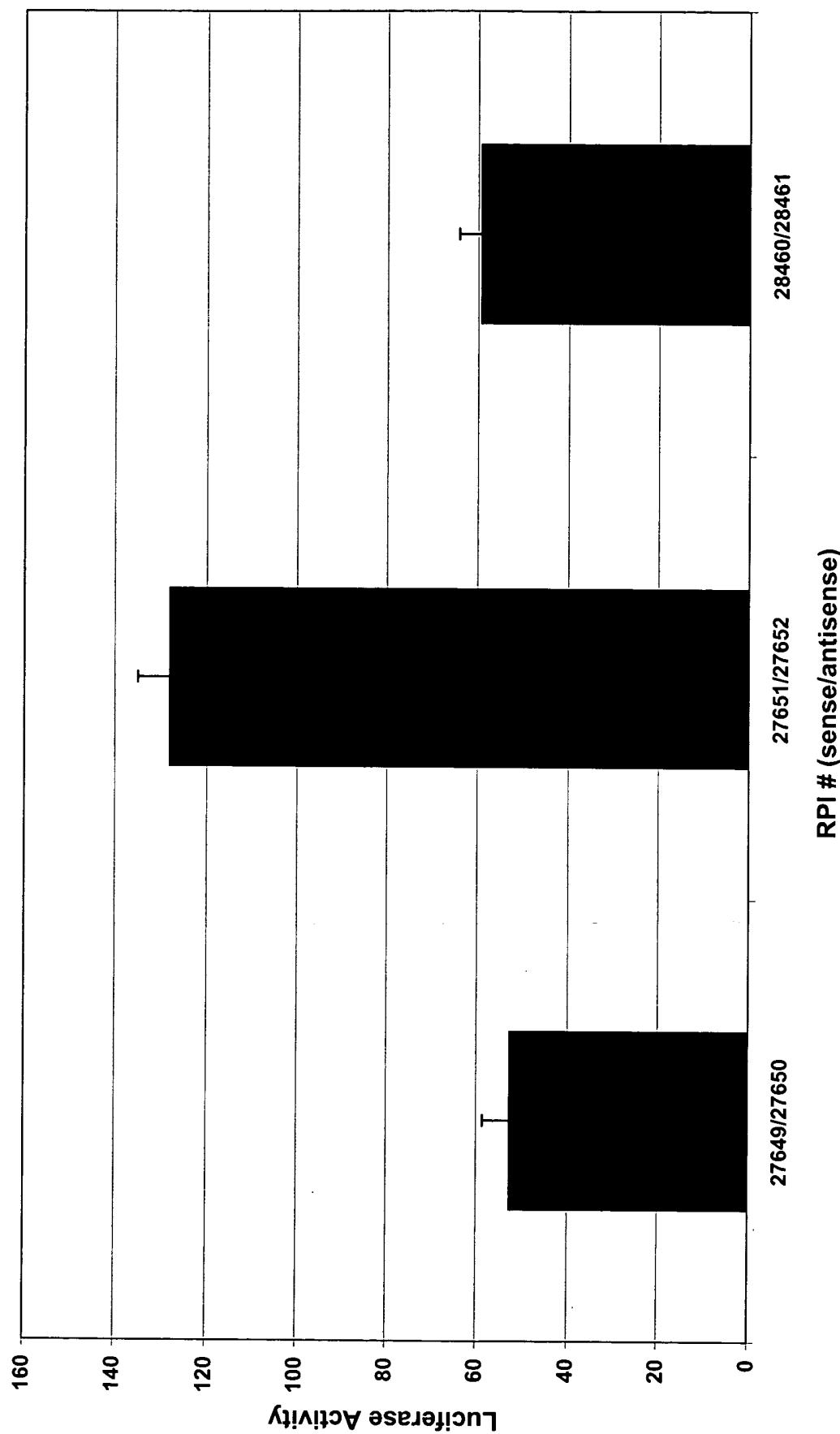


Figure 9

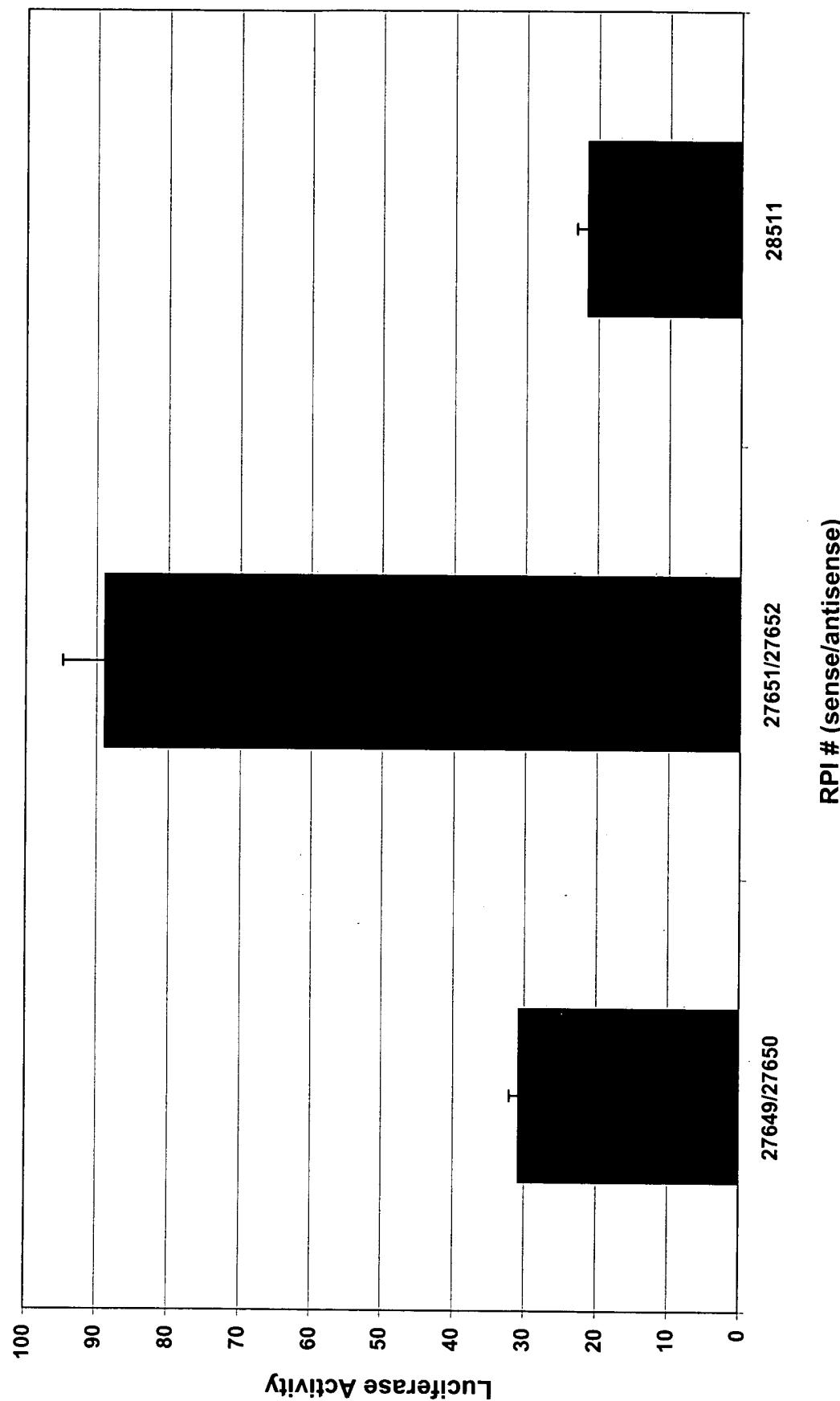


Figure 10

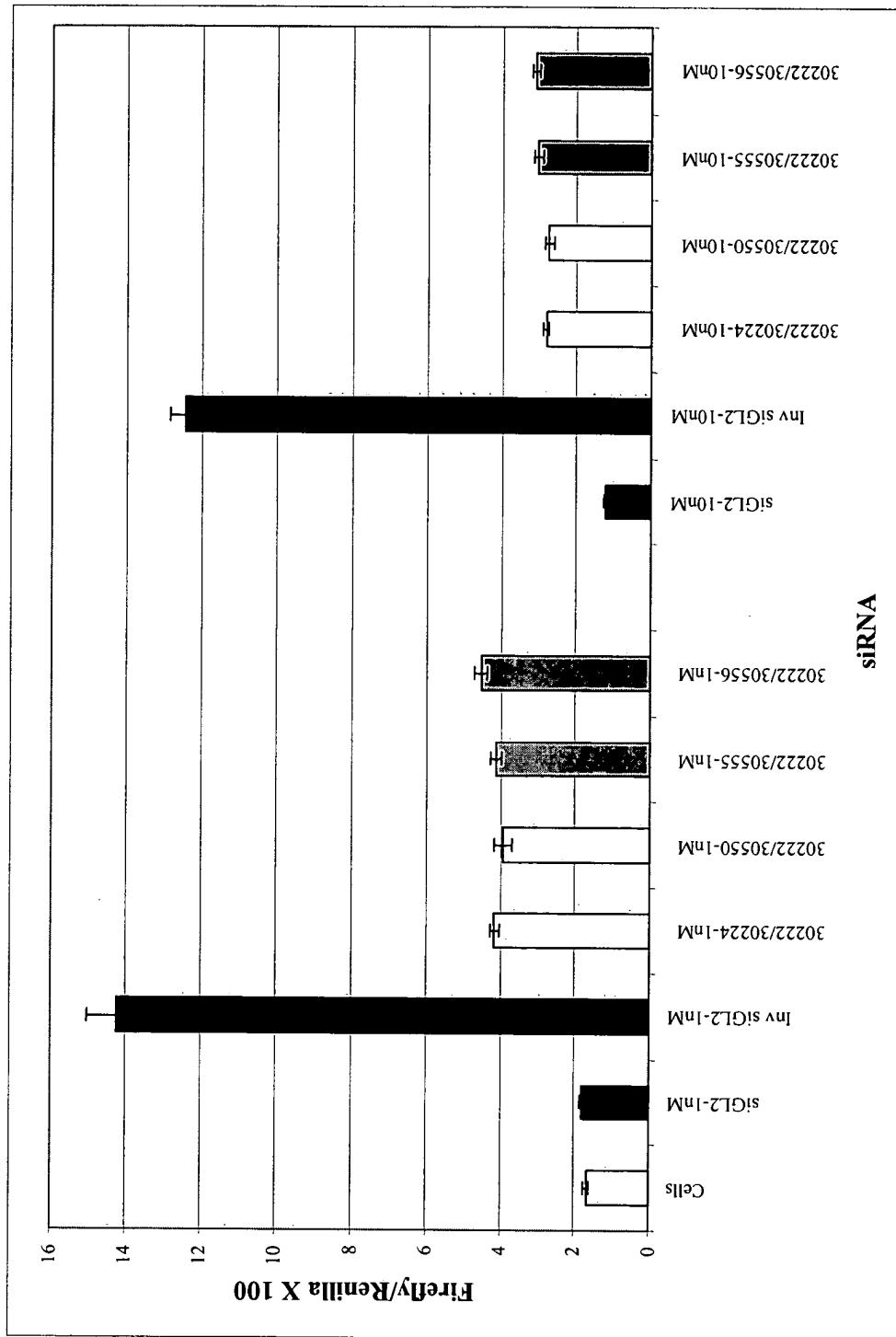


Figure 11

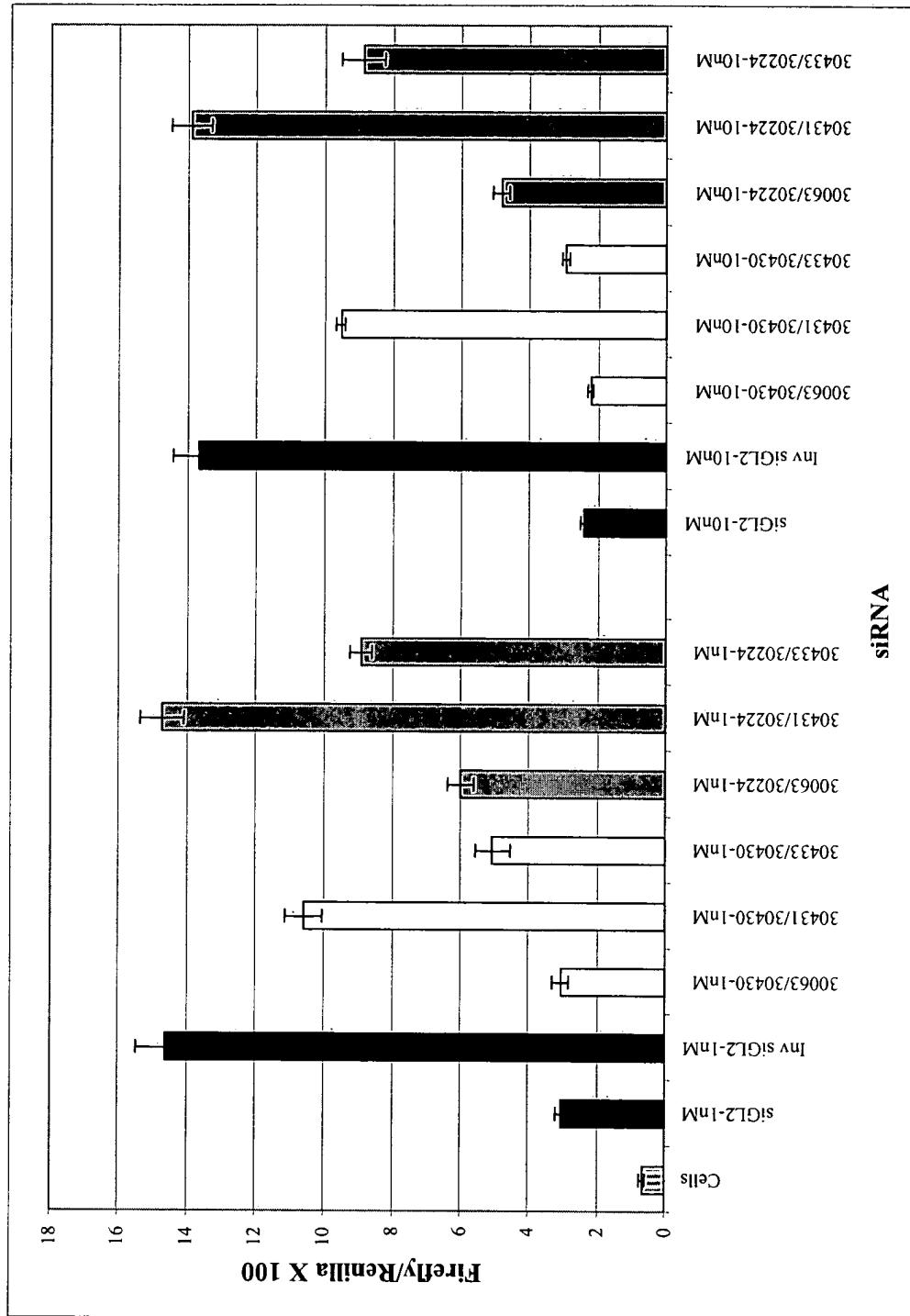


Figure 12

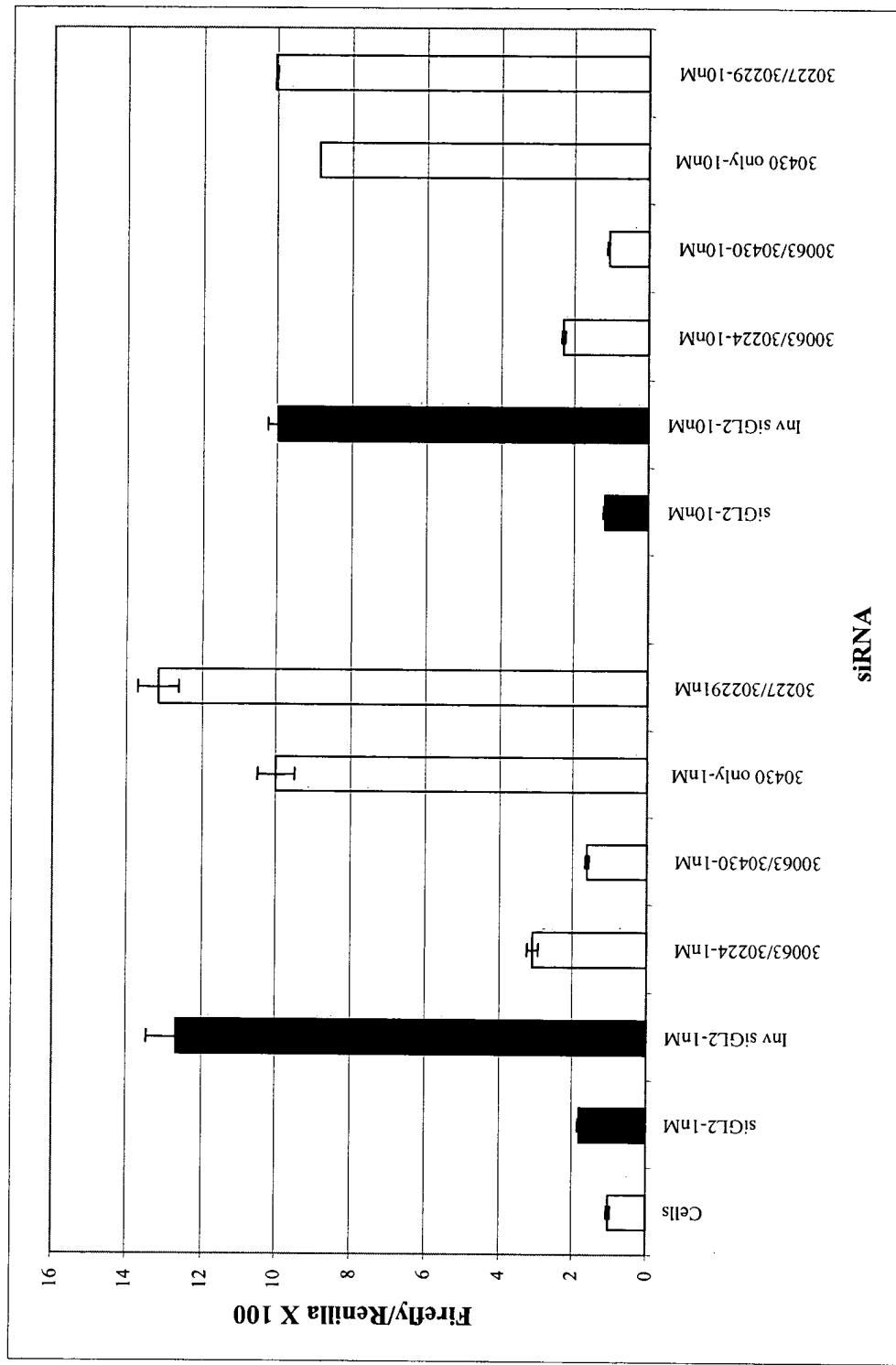


Figure 13

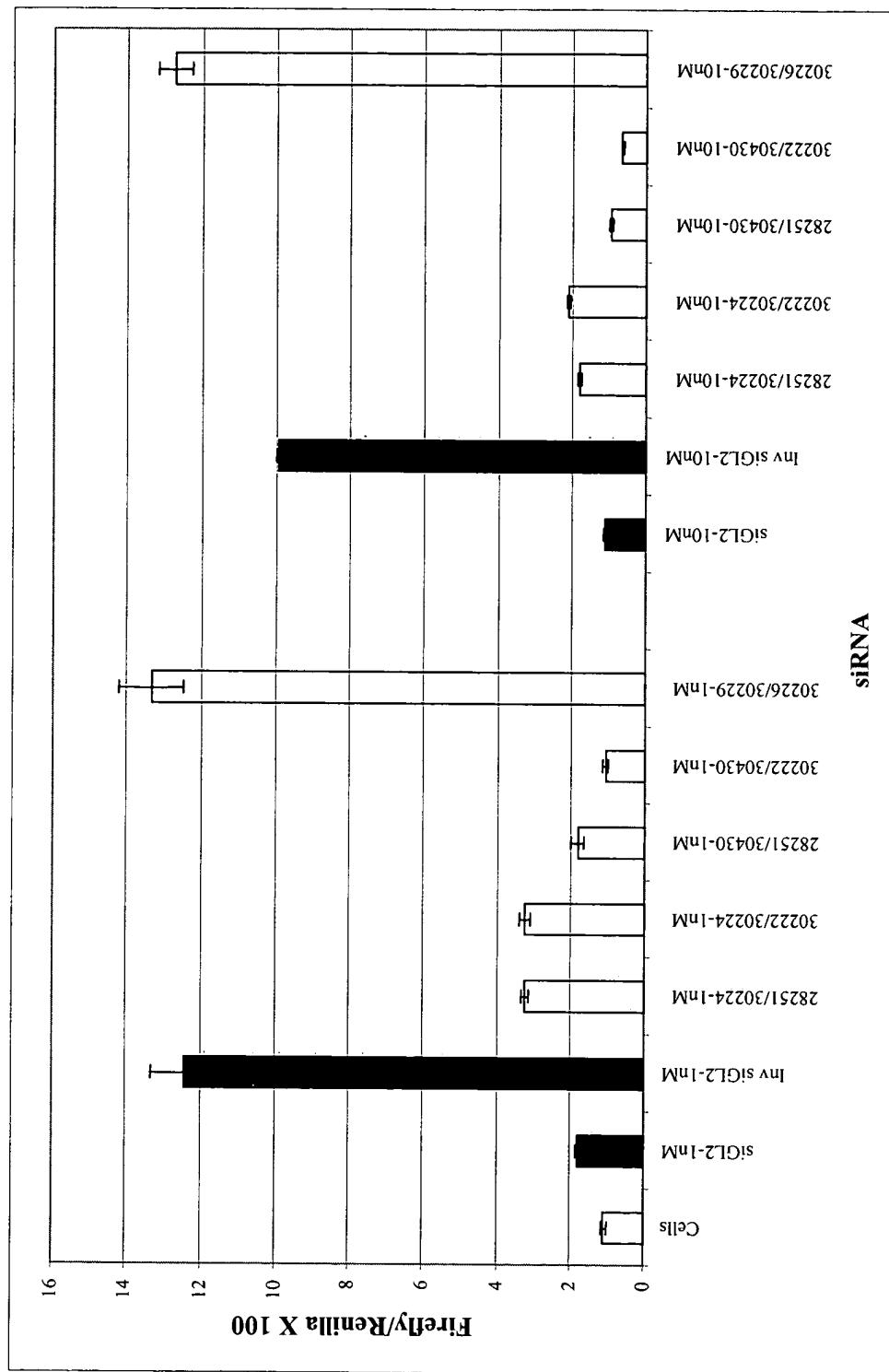


Figure 14

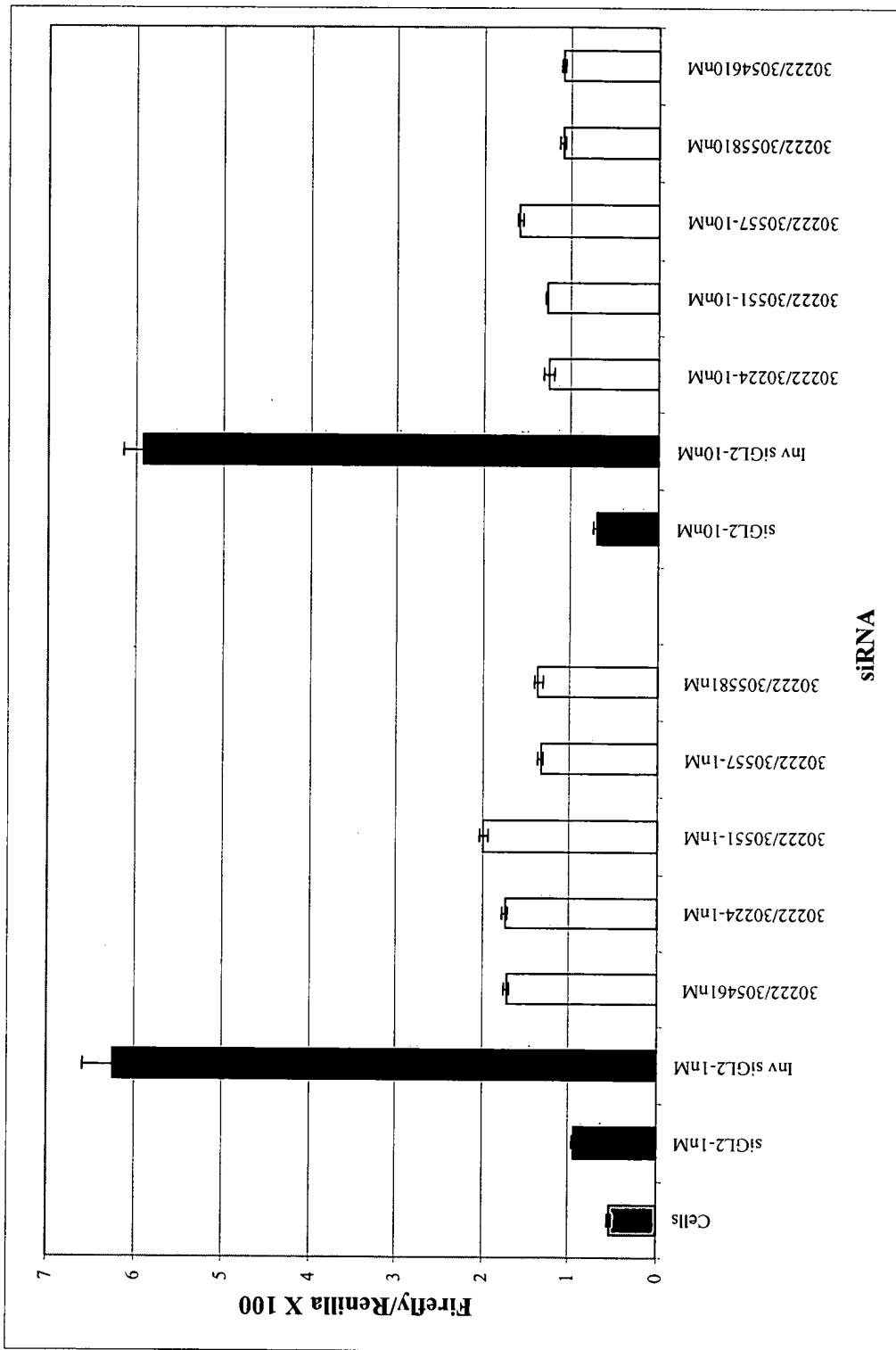


Figure 15

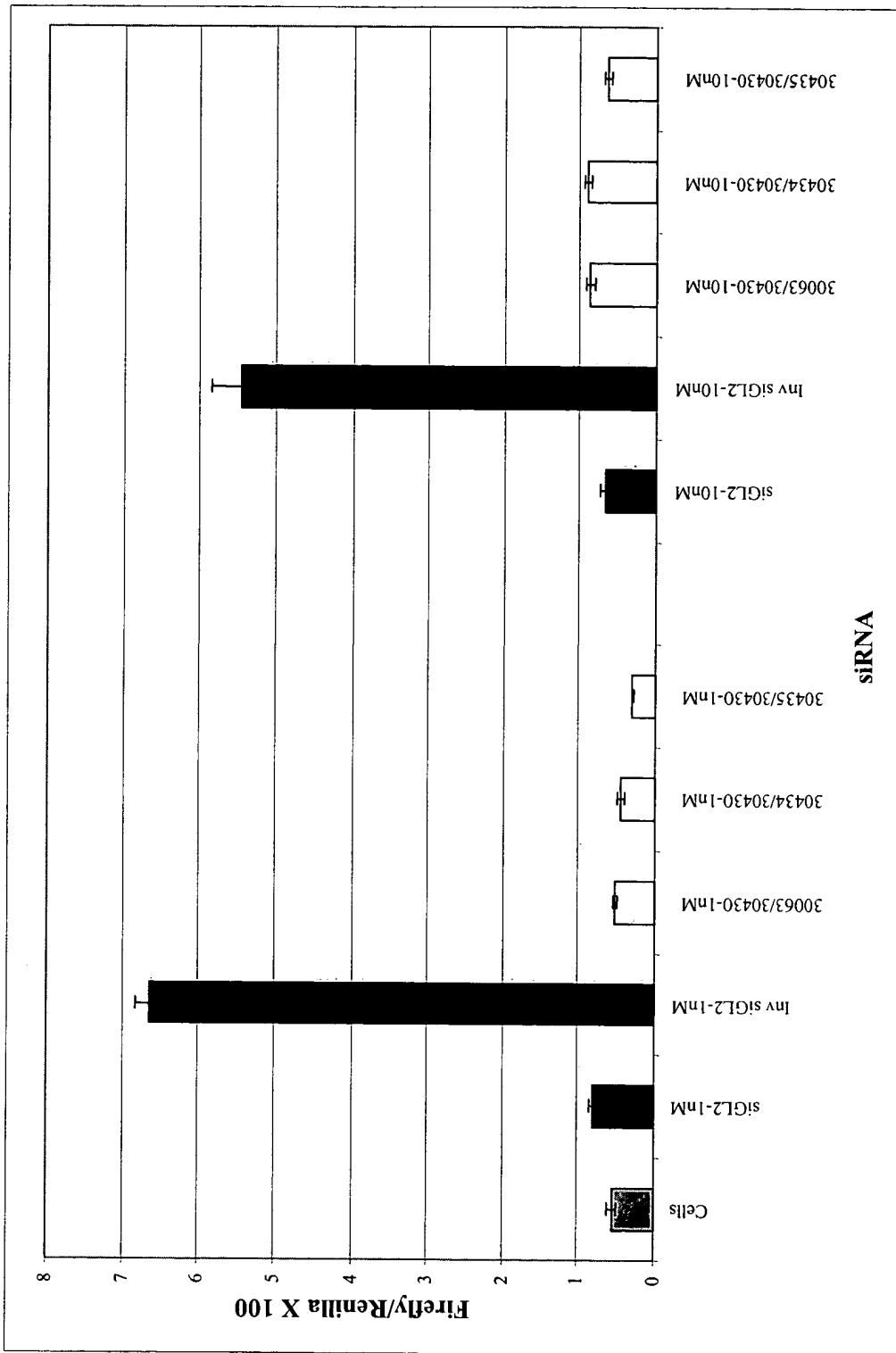


Figure 16

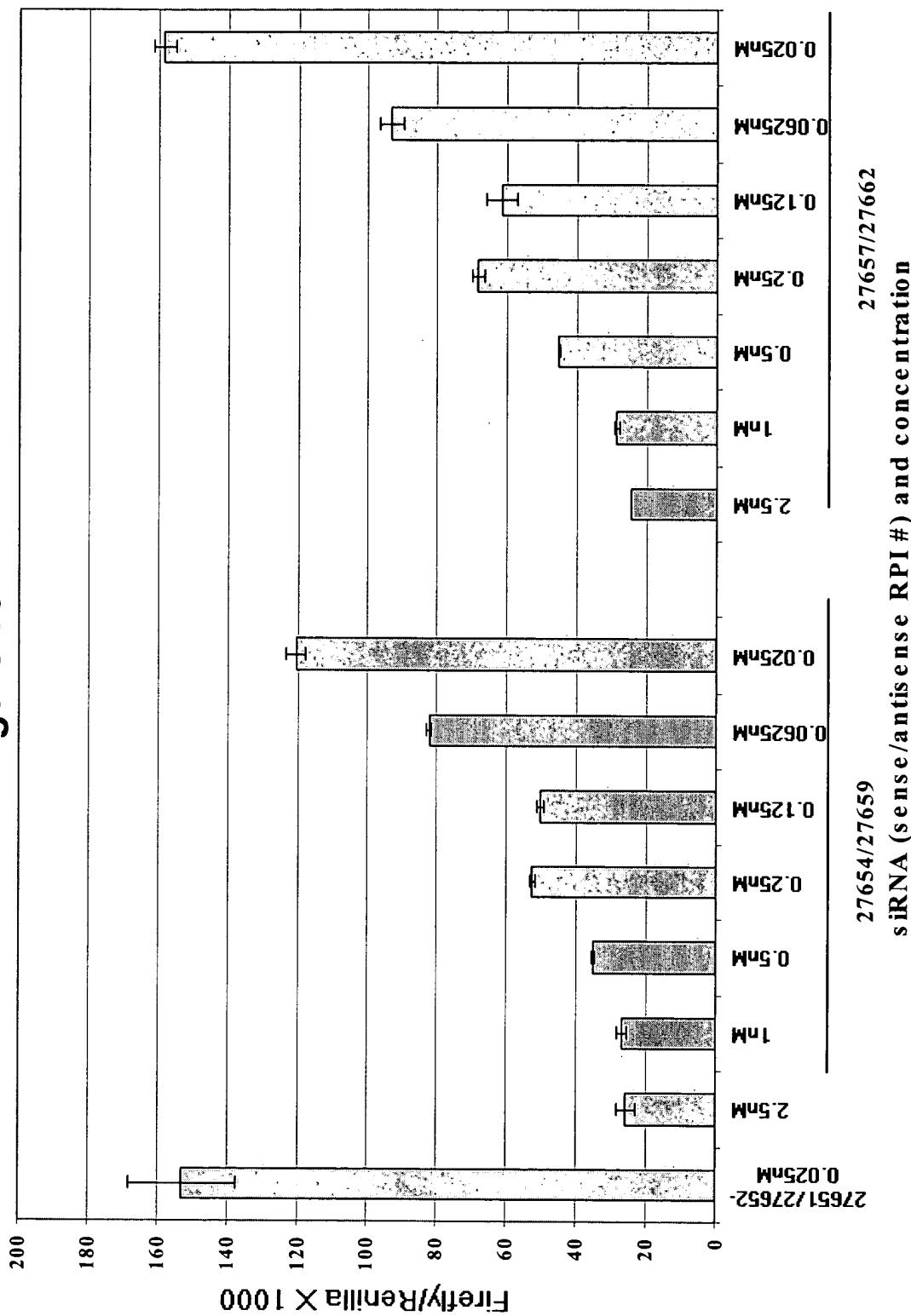


Figure 17

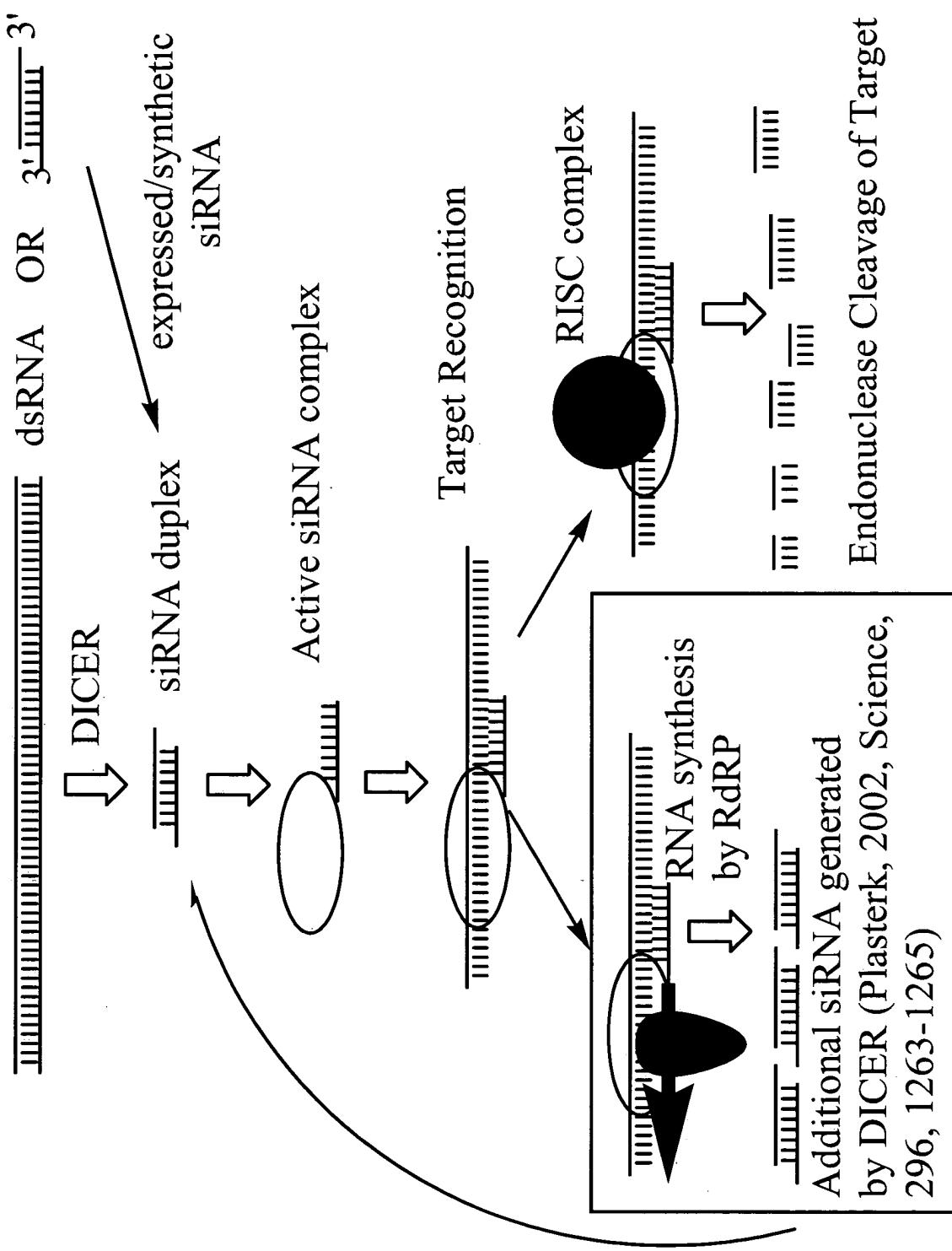
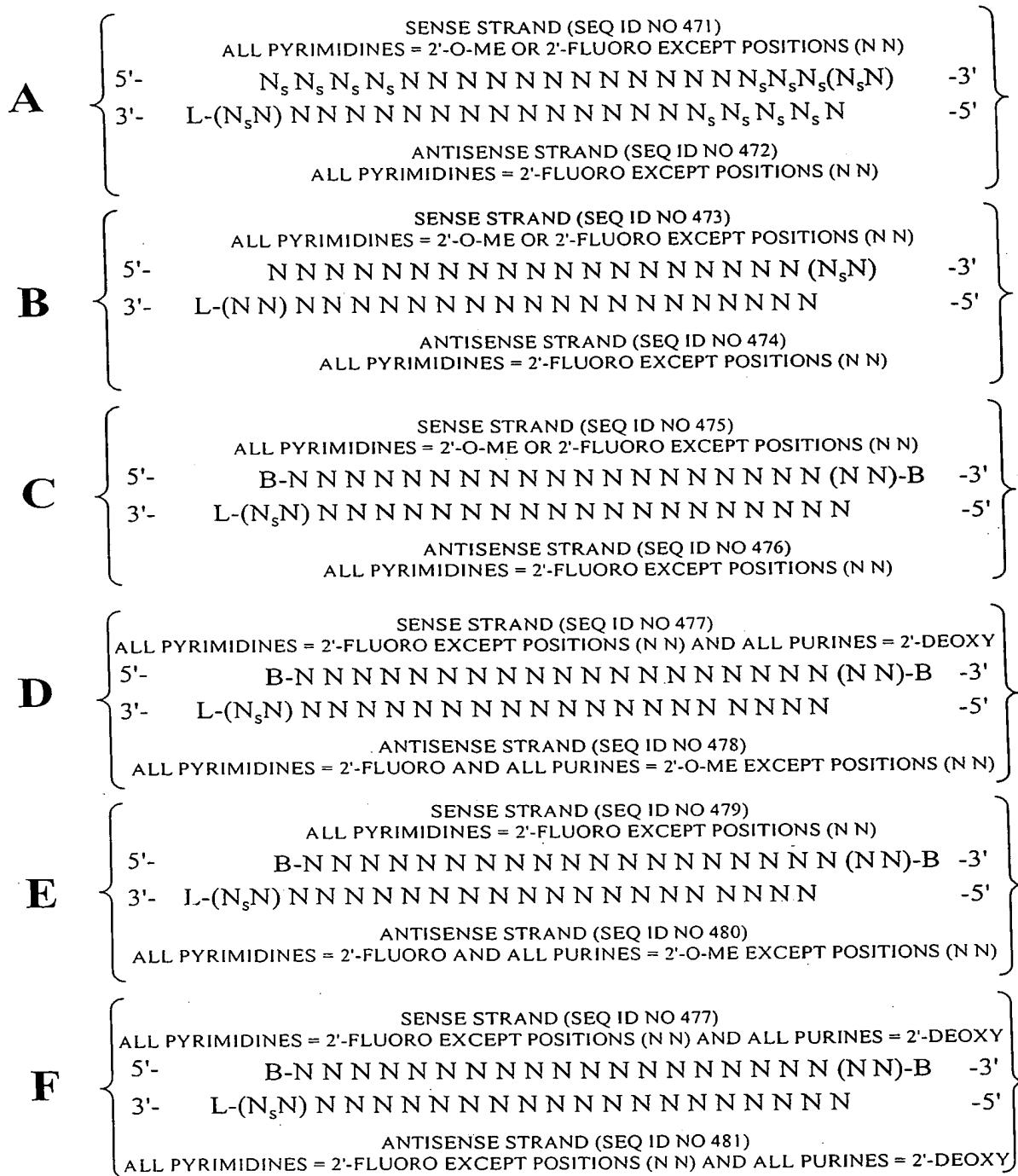


Figure 18



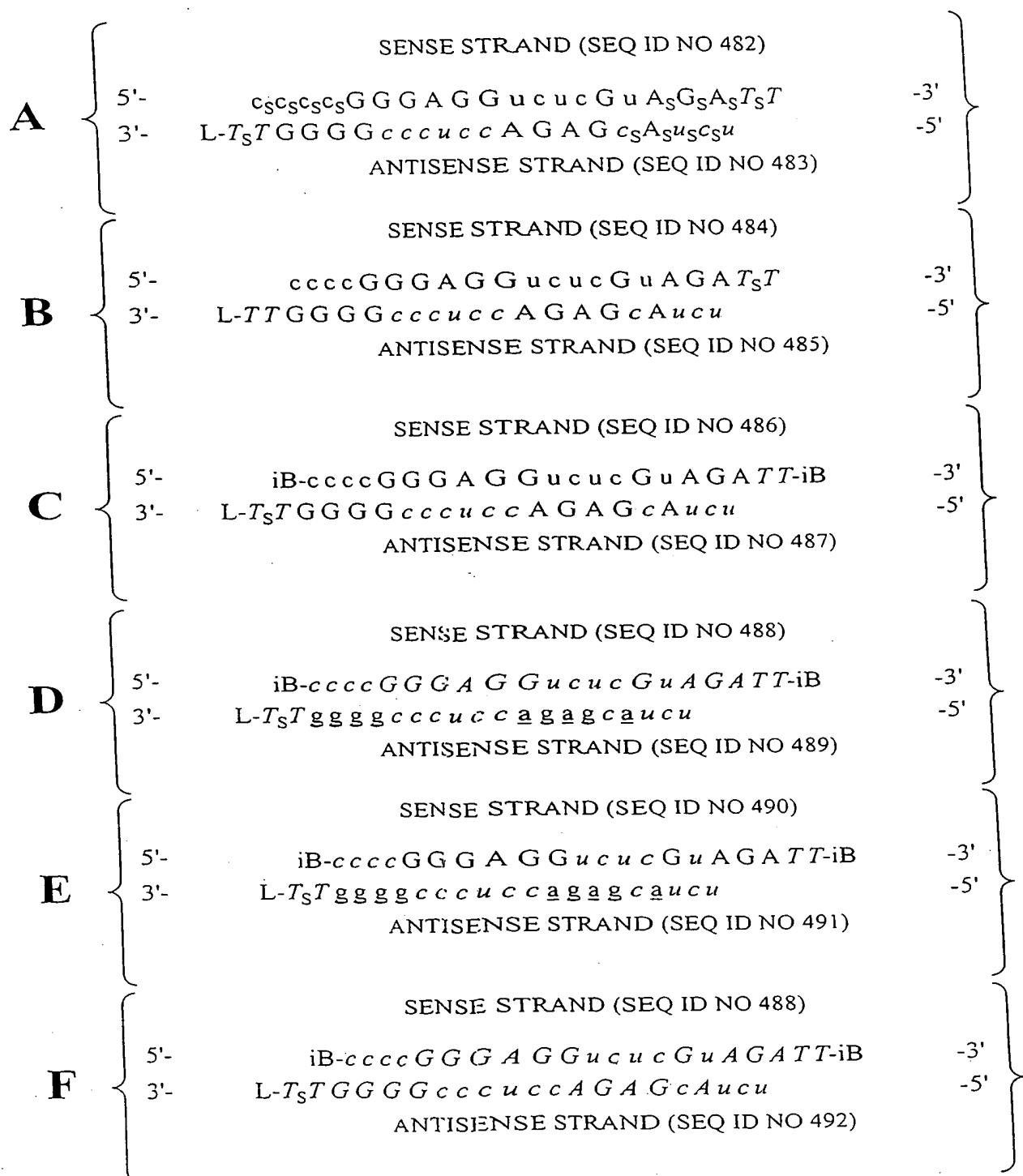
POSITIONS (NN) CAN COMprise ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES

B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENT

L = GLYCERYL MOIETY THAT IS OPTIONAL PRESENT

S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE

Figure 19



lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro

italic lower case = 2'-deoxy-2'-fluoro

underline = 2'-O-methyl

ITALIC UPPER CASE = DEOXY

B = INVERTED DEOXYABASIC

L = GLYCERYL MOIETY OPTIONALY PRESENT

S = PHOSPHOROTHIOATE OR
PHOSPHORODITHIOATE

Figure 20

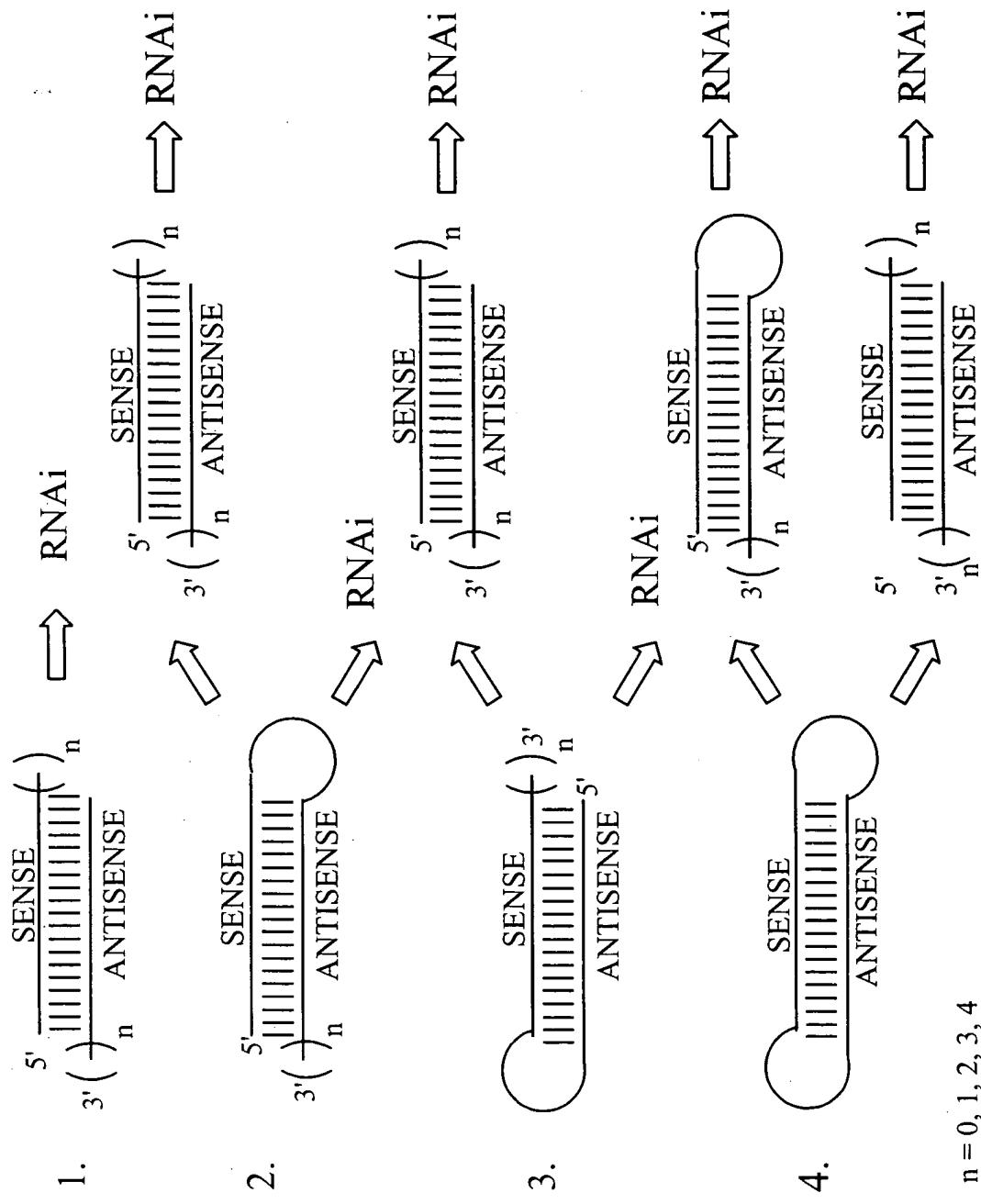


Figure 21: Target site Selection using siRNA

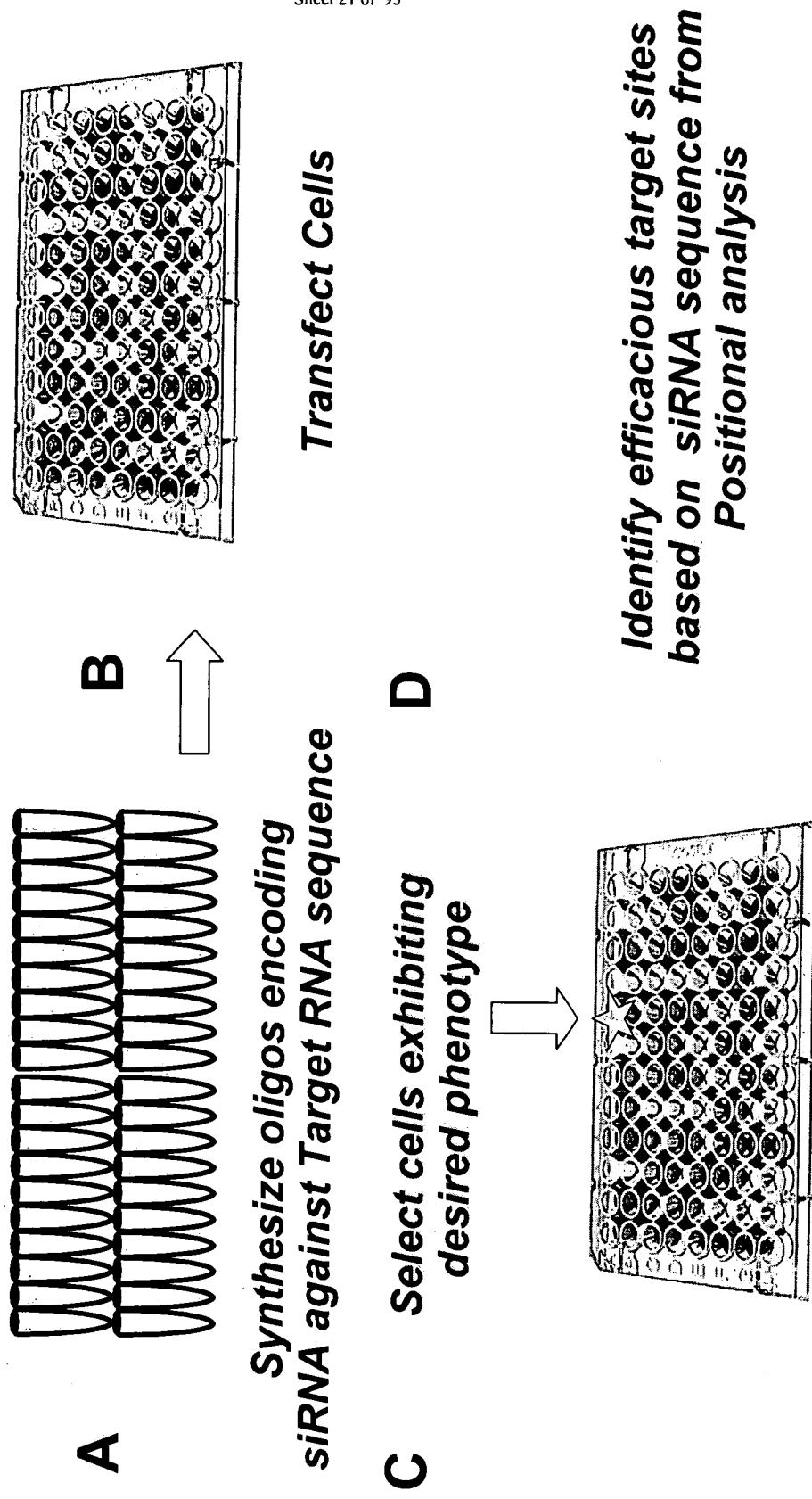
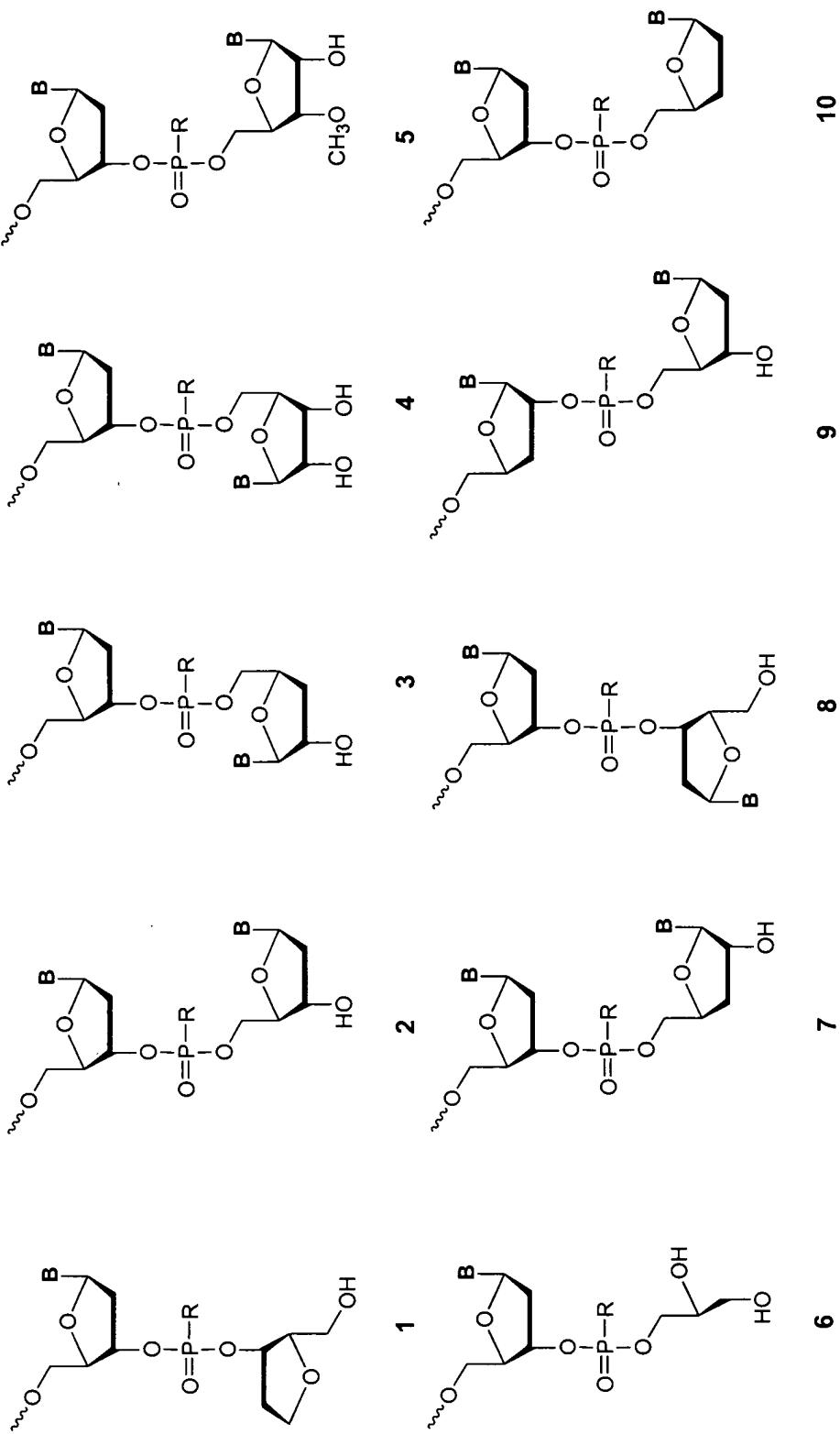
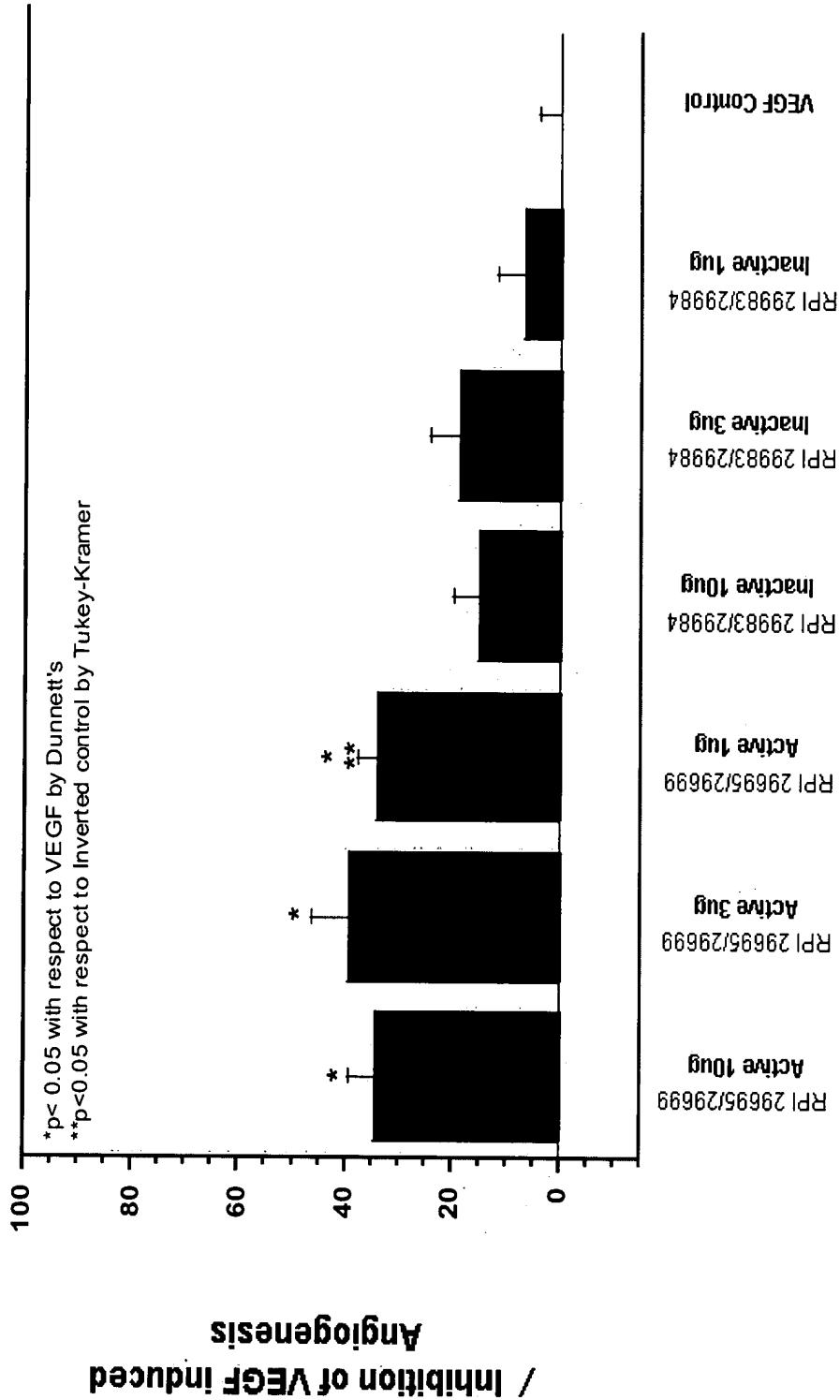


Figure 22



R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl
B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

Figure 23: Inhibition of VEGF-Induced Angiogenesis by siRNAs



**Figure 24: Stab4/5 siNA Targeted to HBV:
HBsAg Levels in Hep G2 Cells:**

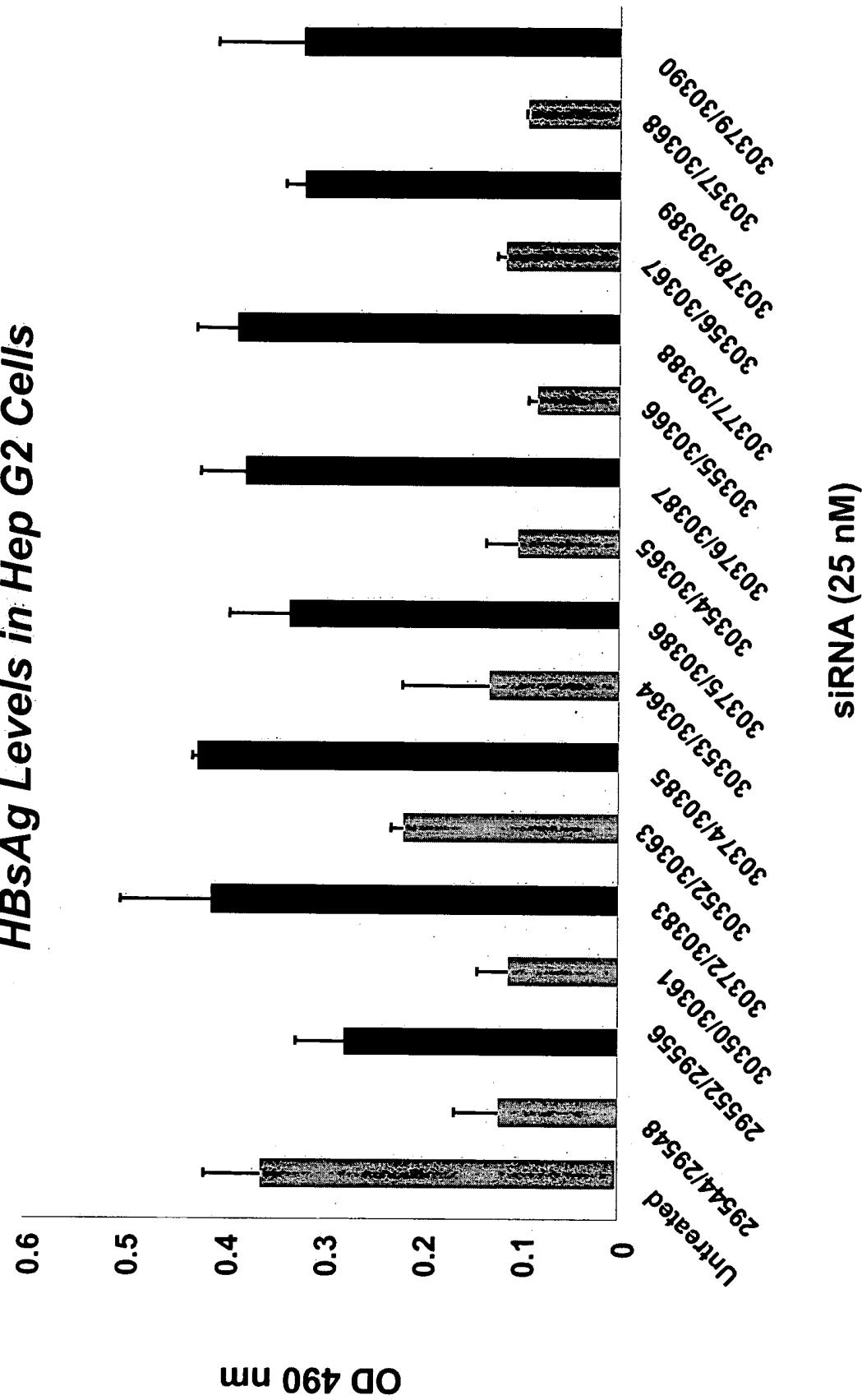


Figure 25: Dose Response with Stab4/5 siRNAs Targeted to HBV Sites 262 & 1580

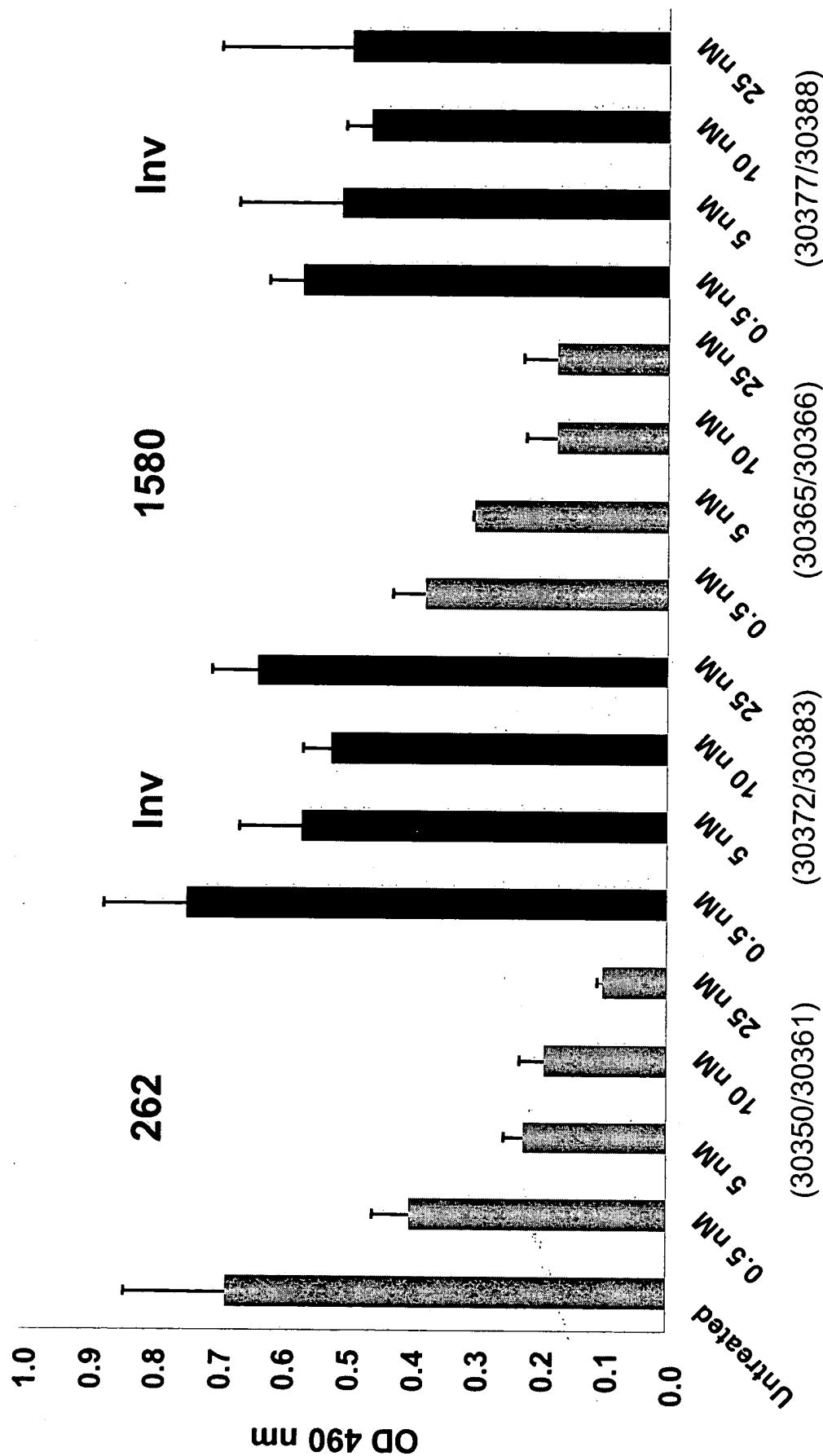


Figure 26: Comparison of Stab7/8 and Stab 7/11 siRNAs Targeted to HBV RNA Site 1580

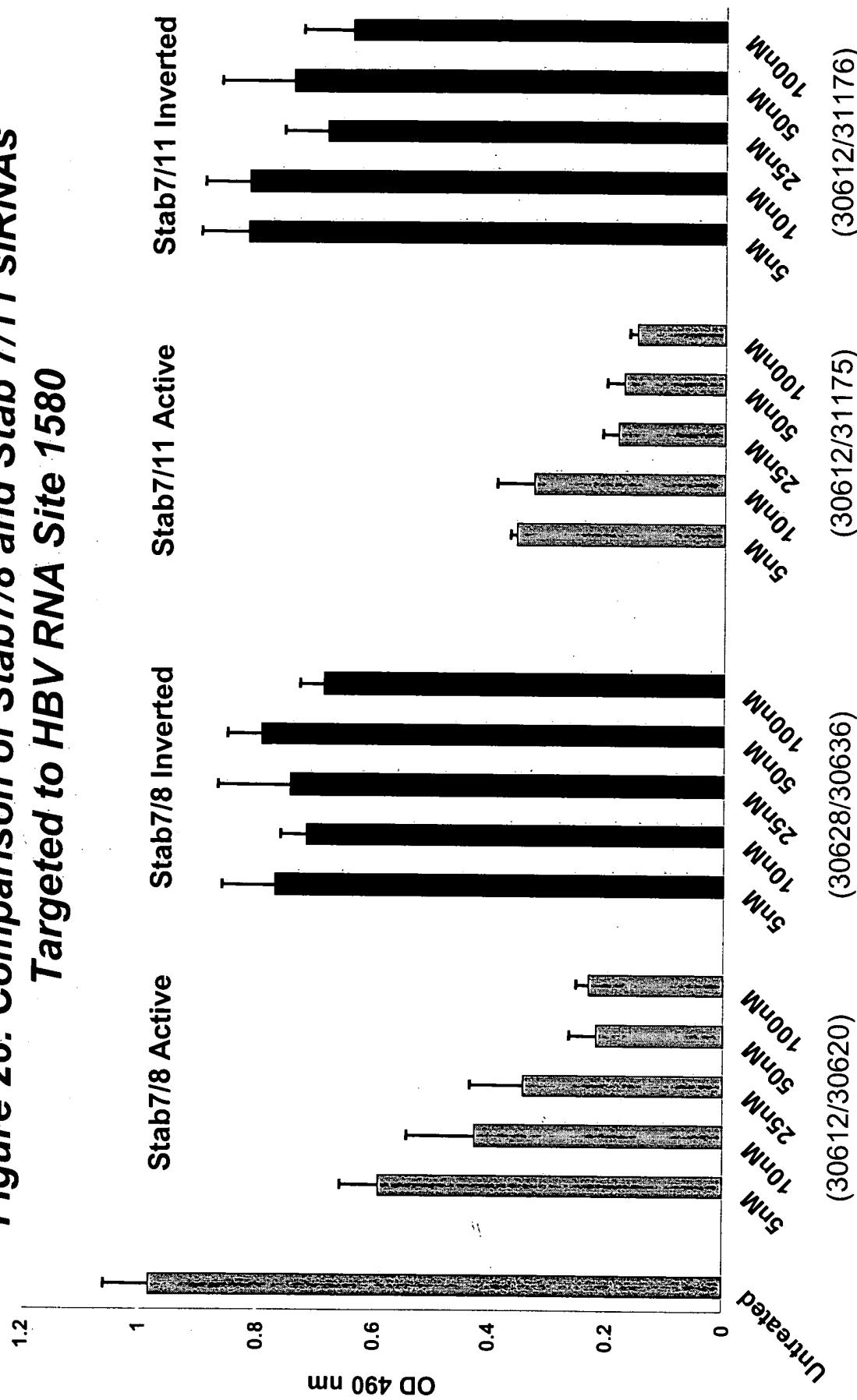
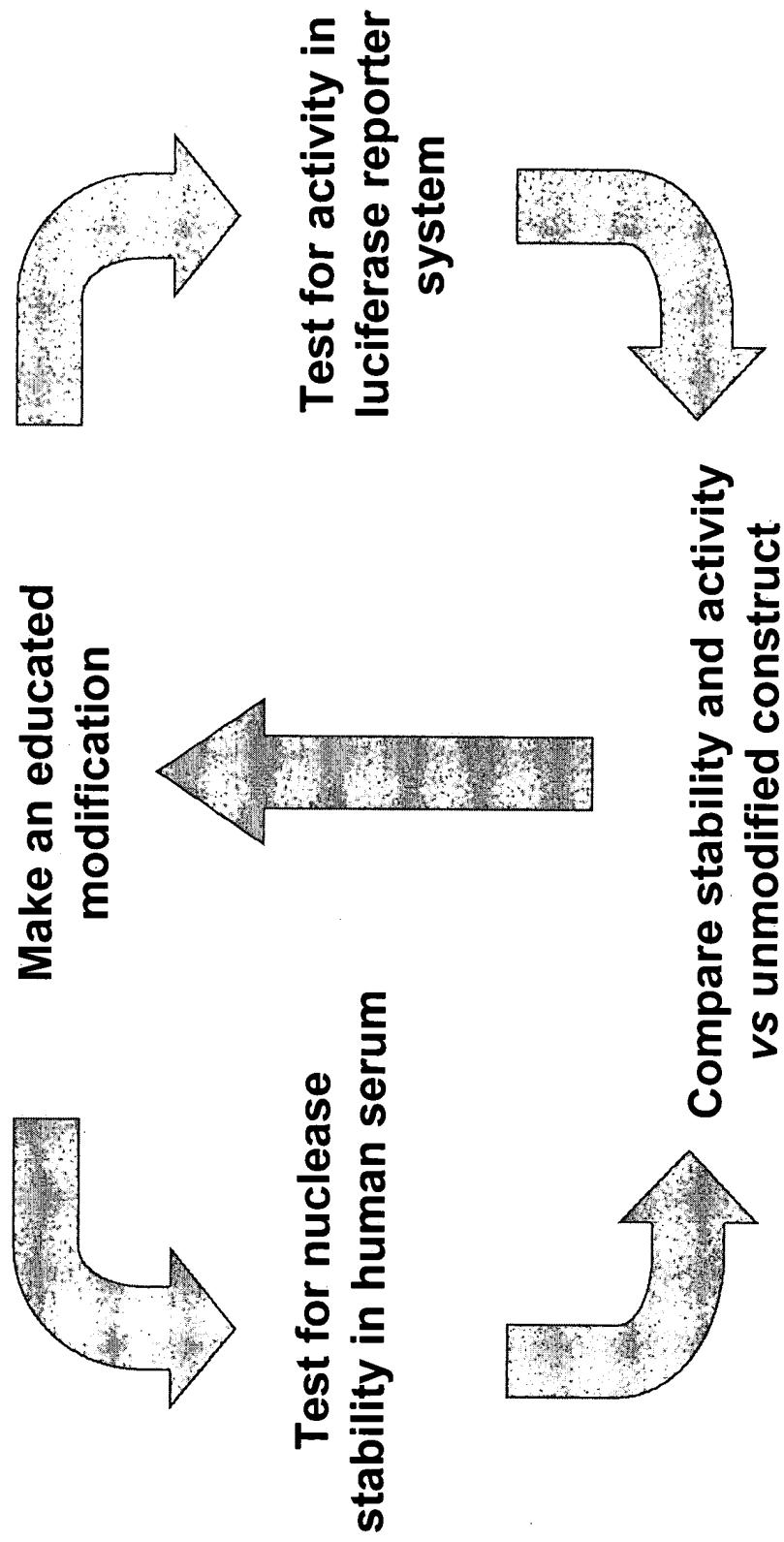


Figure 27: Modification Strategy



**Figure 28: Duration of siRNA Effect
All-Ribo vs. Stab4/5 HBV Site 1580: HBsAg Levels**

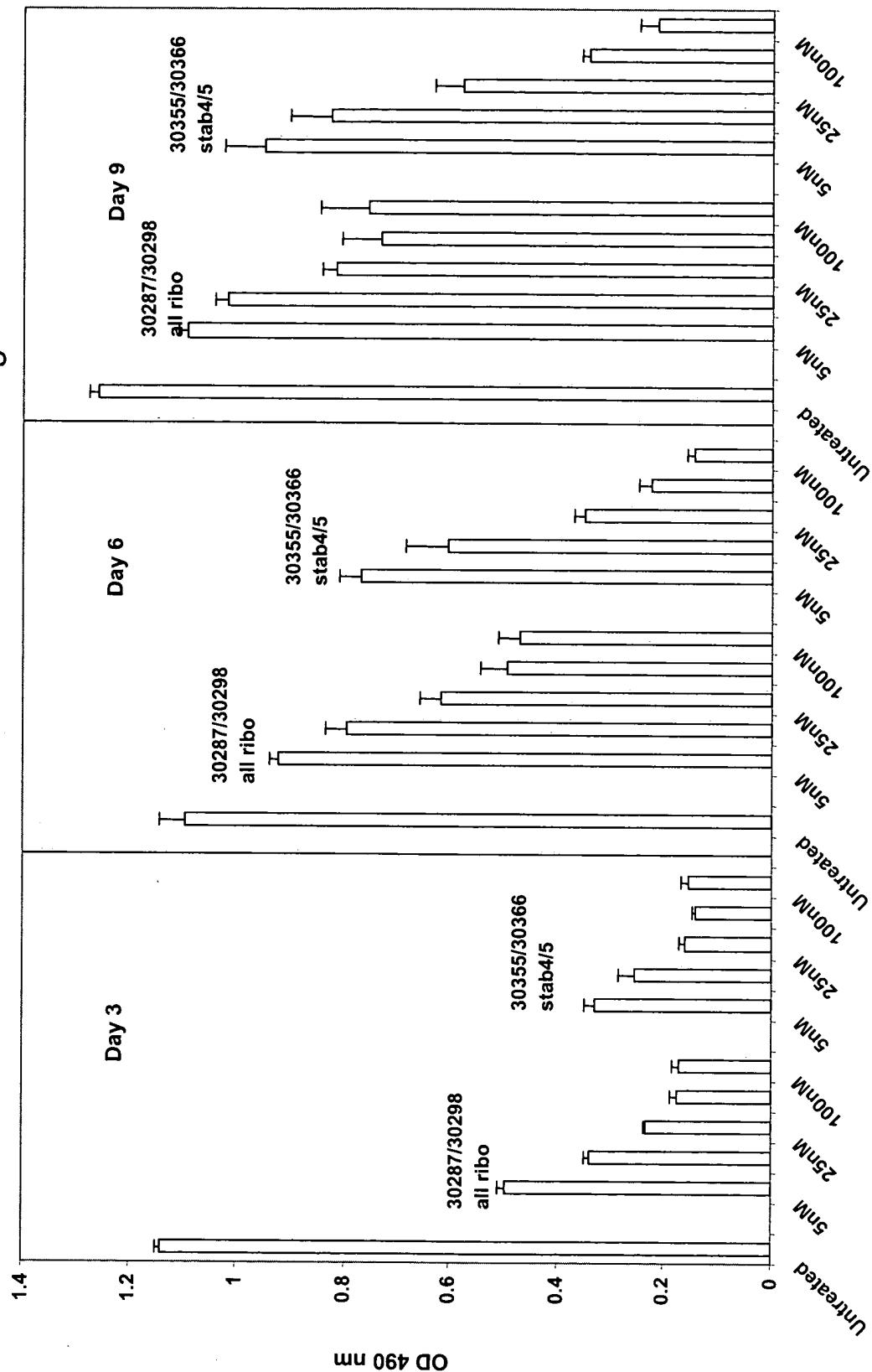


Figure 29: Duration of siRNA Effect
All-Ribo vs. Stab7/8 HBV Site 1580: HBsAg Levels

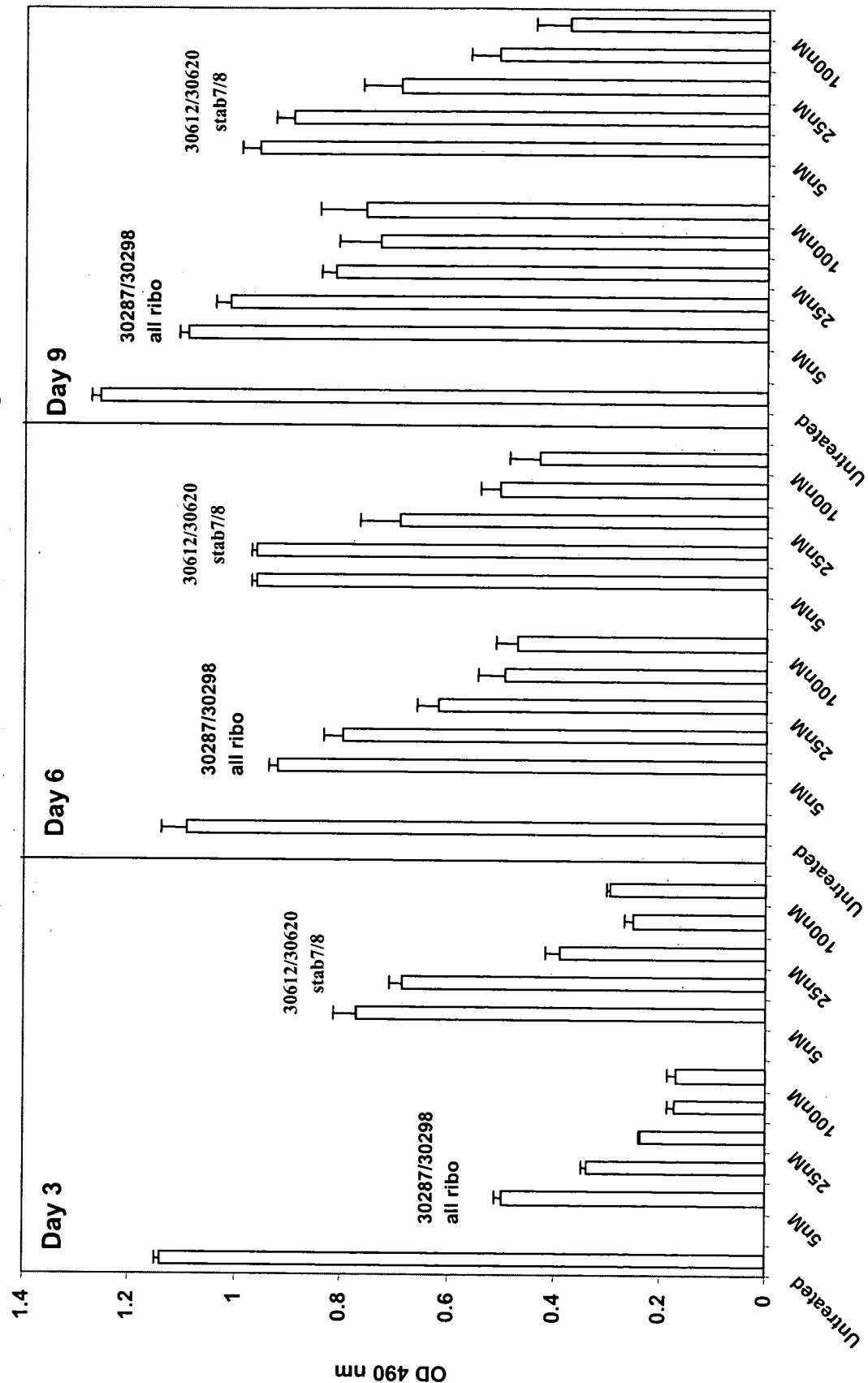
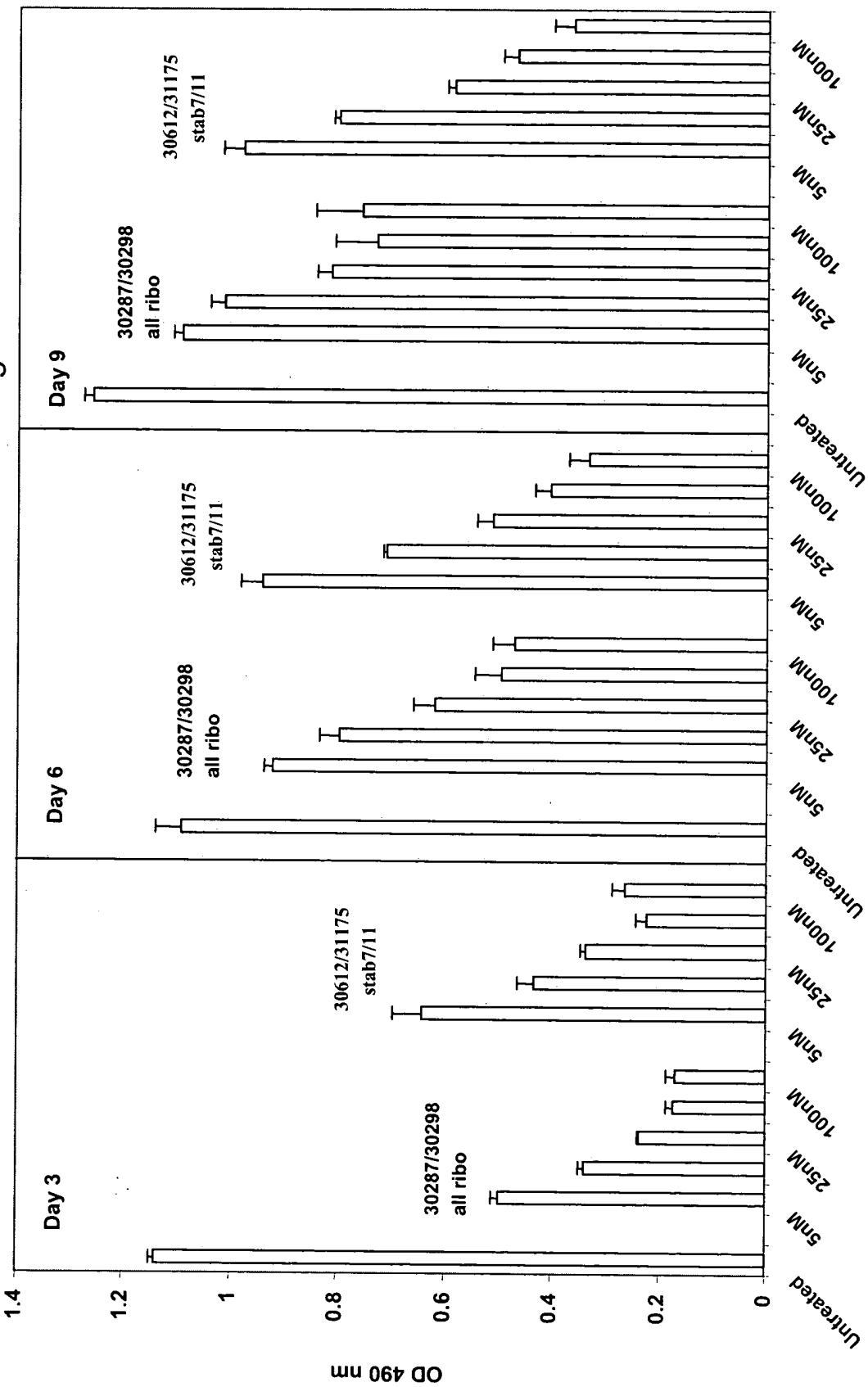


Figure 30: Duration of siRNA Effect
All-Ribo vs. Stab7/11 HBV Site 1580: HBsAg Levels



**Figure 31: Duration of siRNA Effect
All-Ribo vs. Stab9/10 HBV Site 1580: HBsAg Levels**

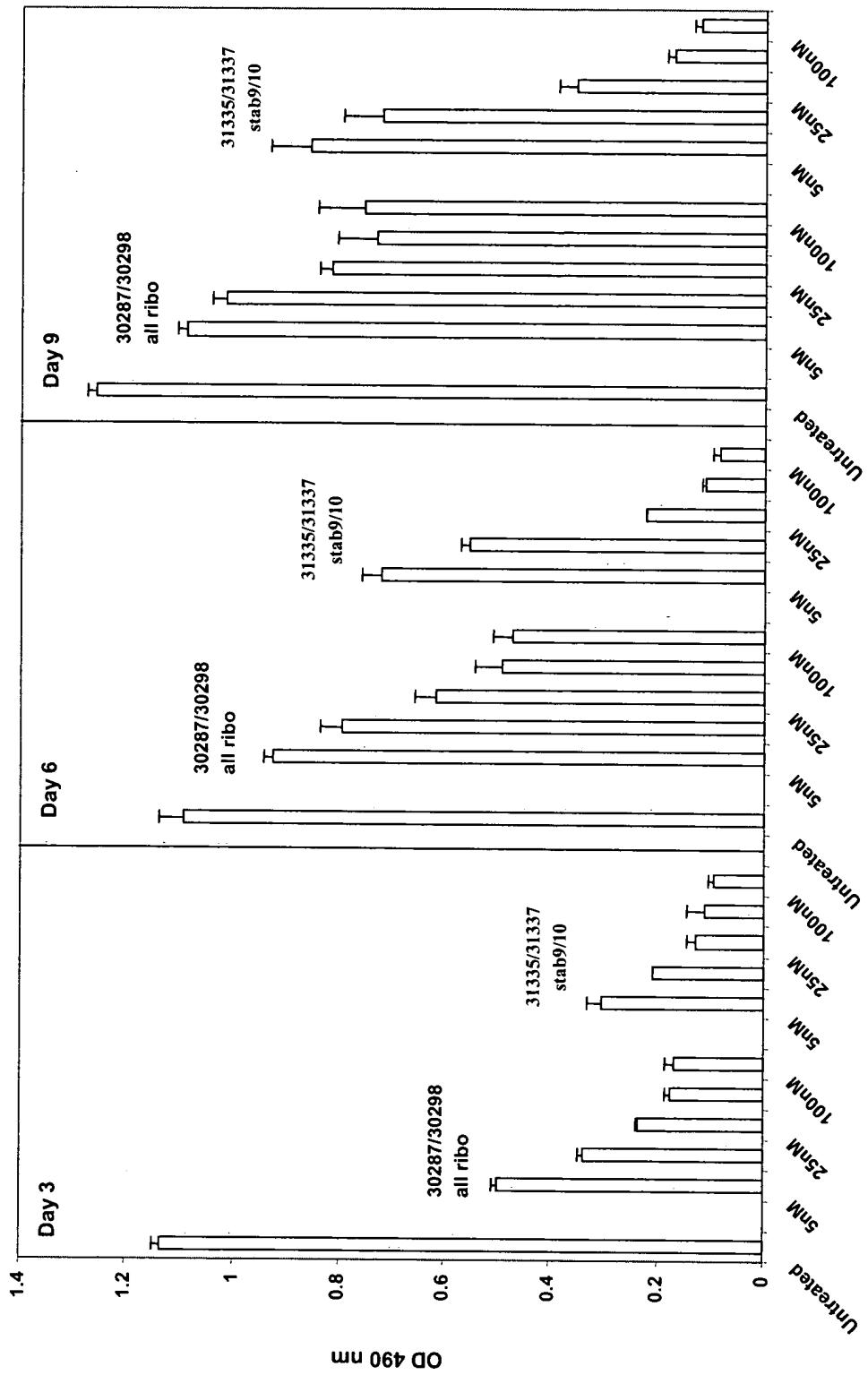


Figure 32 : siRNAs targeting HCV chimera

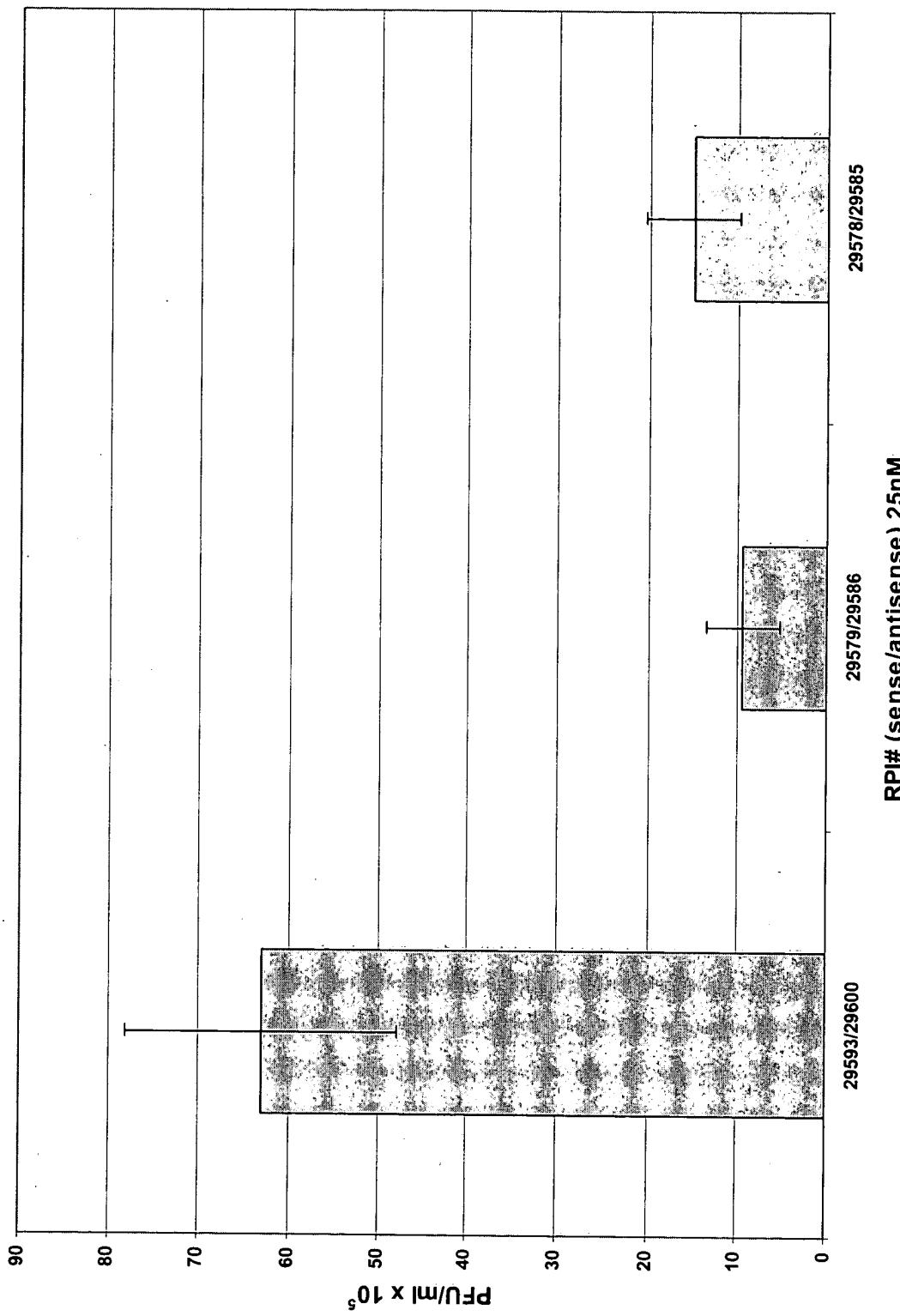


Figure 33: HCV siRNA dose response

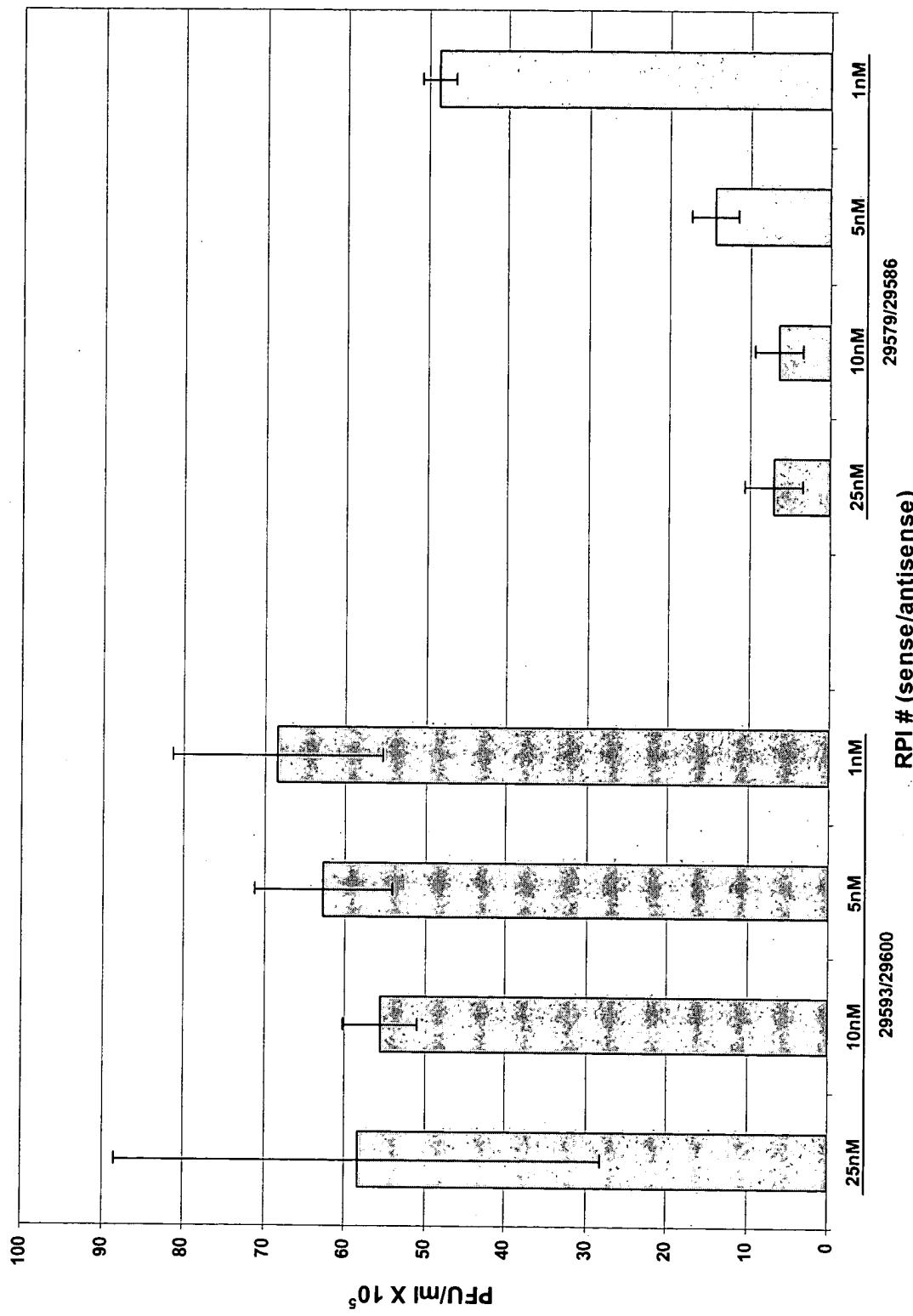


Figure 34: Chemically Modified siRNA targeting HCV chimera

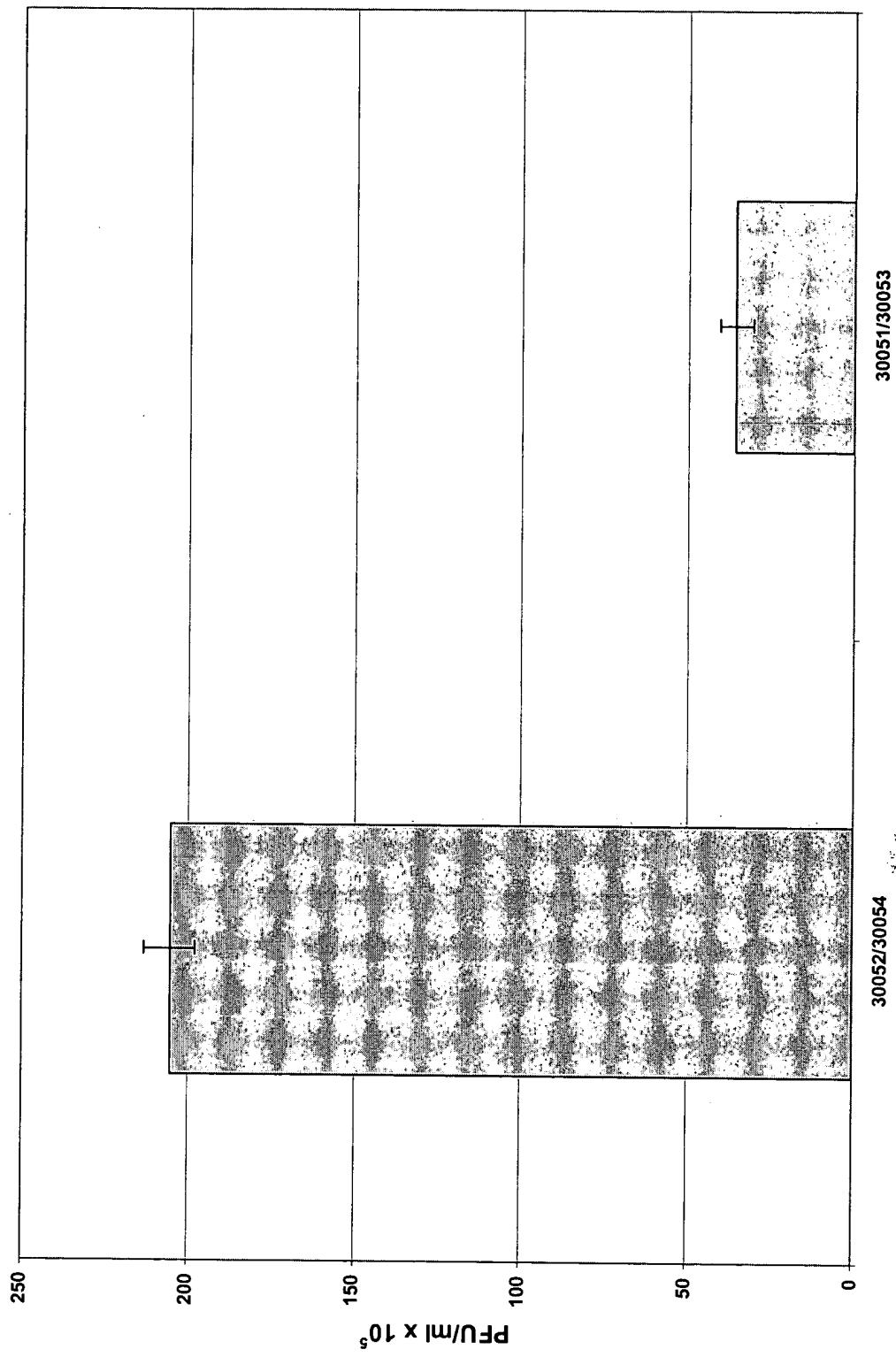


Figure 35: Chemically Modified siRNA targeting HCV chimera

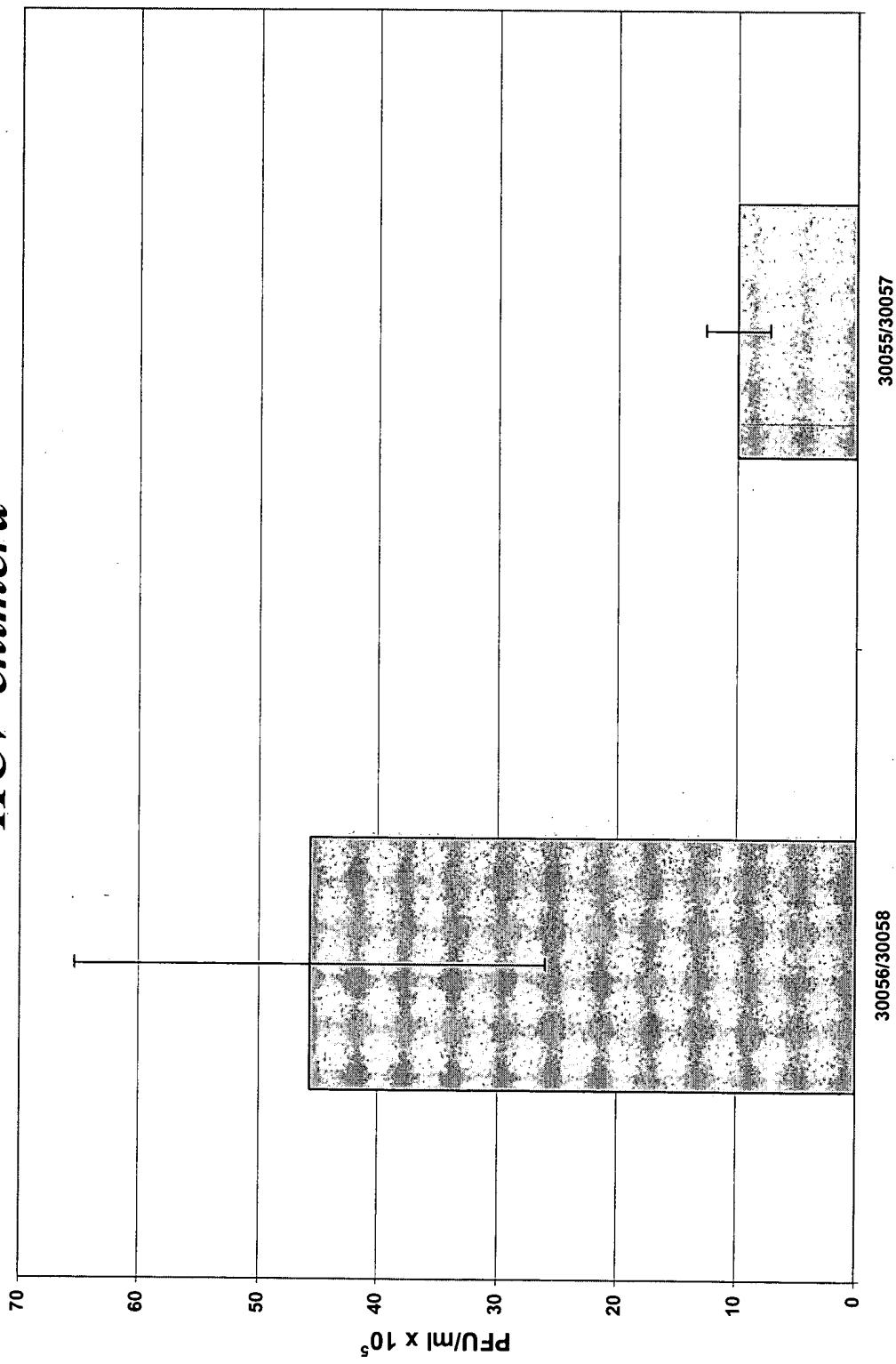


Figure 36: Chemically Modified siRNA targeting HCV chimera

HCV/PV#280-siRNA to HCV-Luc 325/345

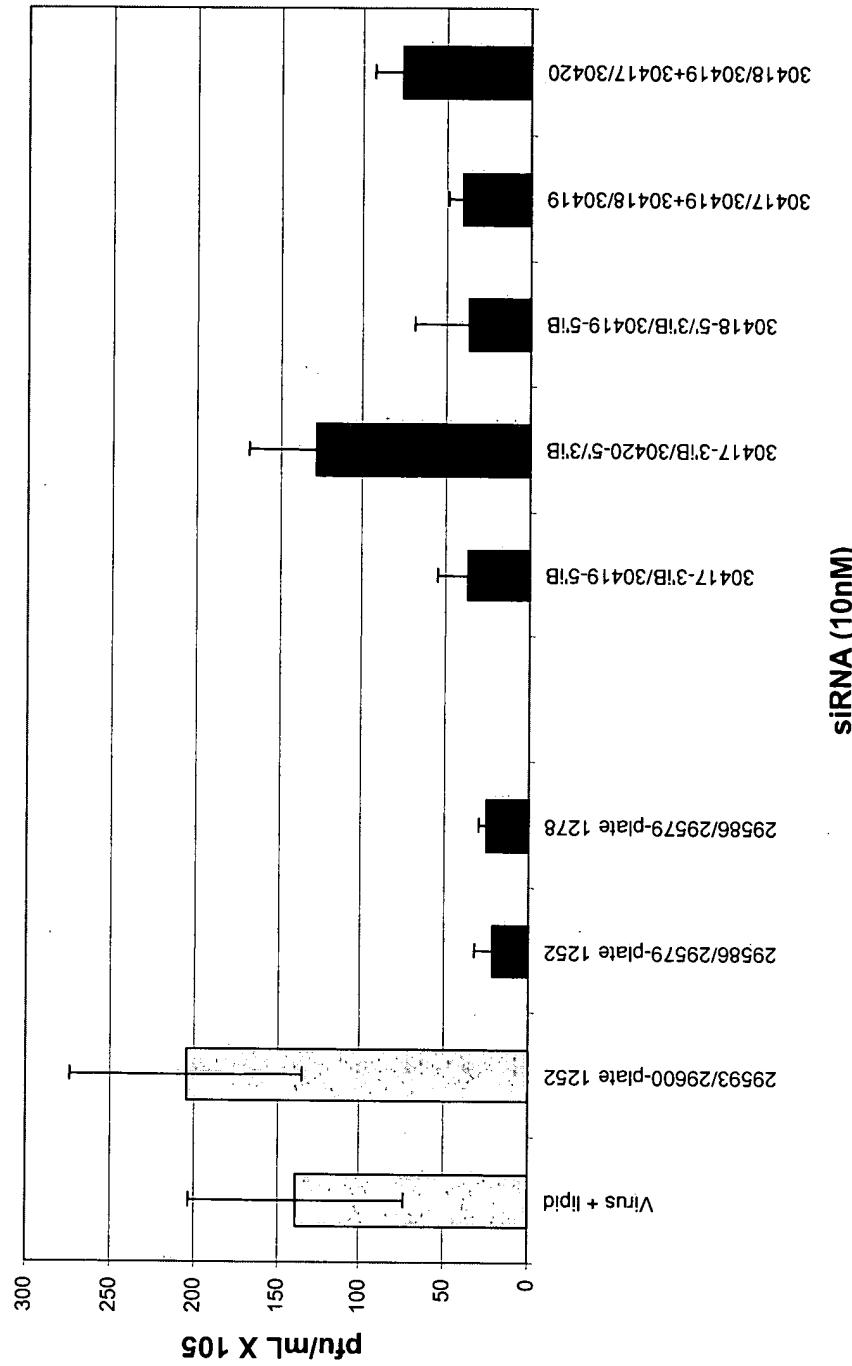


Figure 37: Chemically Modified siRNA targeting HCV chimera

HCV/PV#280-siRNA to HCV-Luc site 325/345

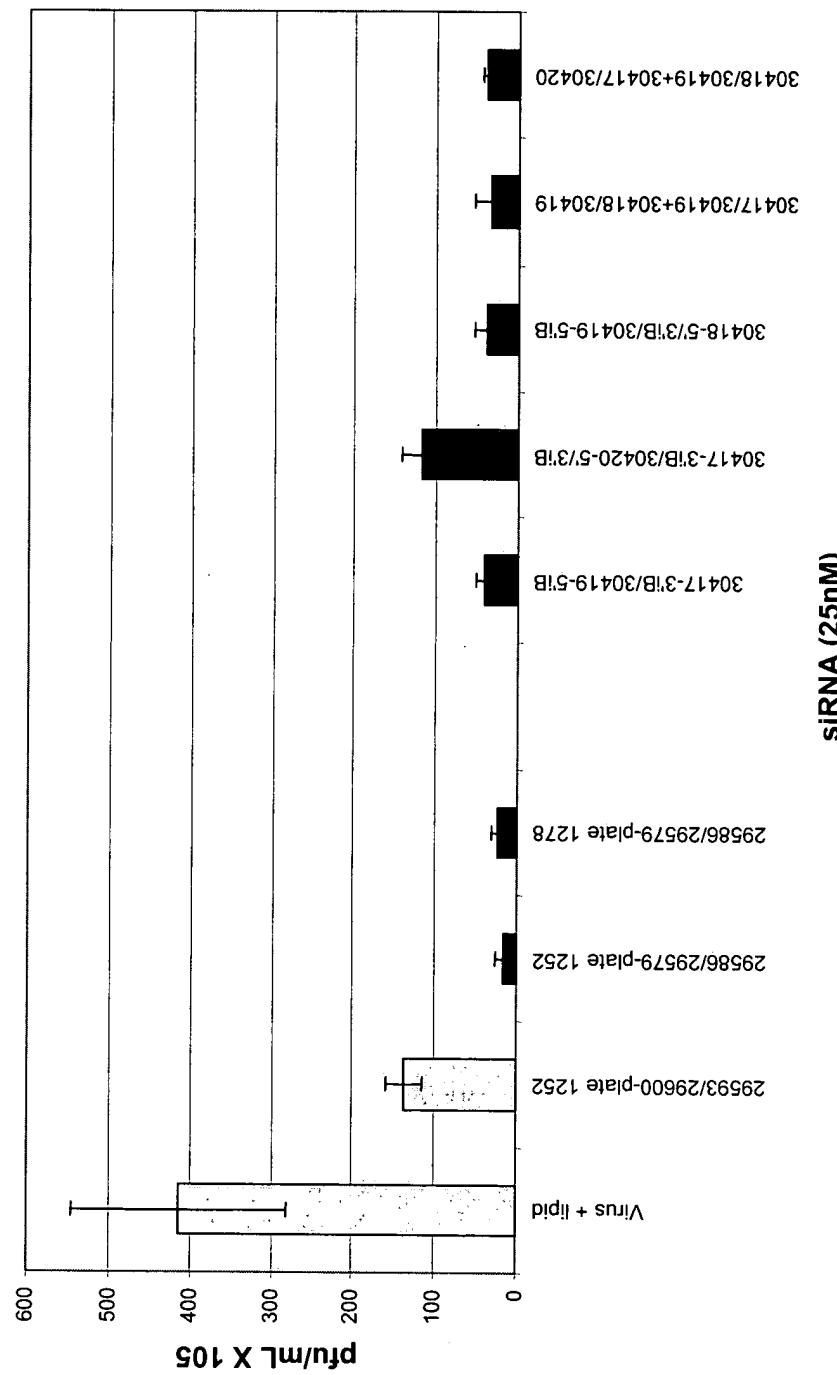


Figure 38: HCV/Replicon Cells transfected with 0.5 μl/well LFA 2K-72 hours

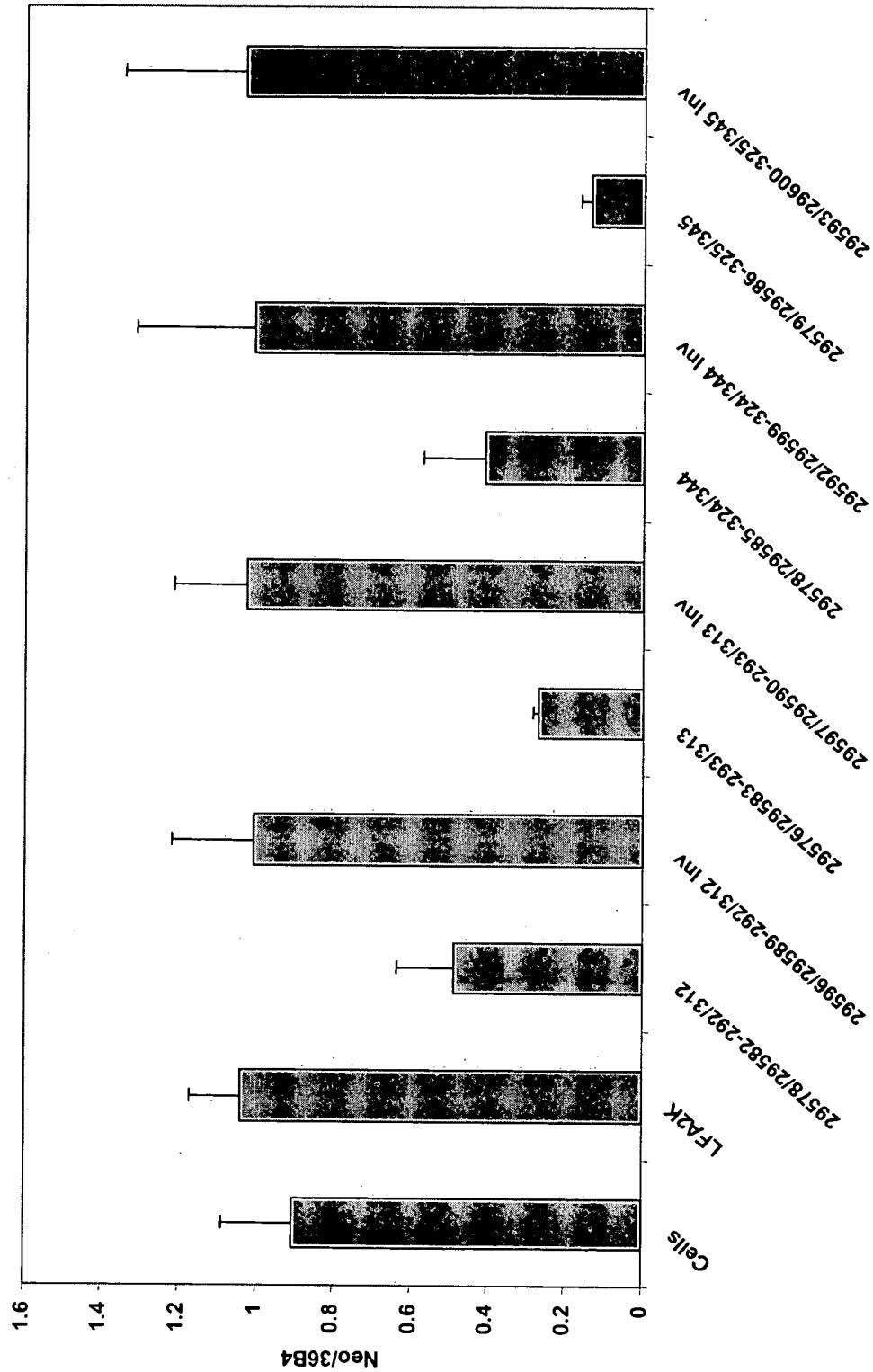


Figure 39: Dose Response with Stab4/5 siNA Leads in HCV Subgenomic Replicon

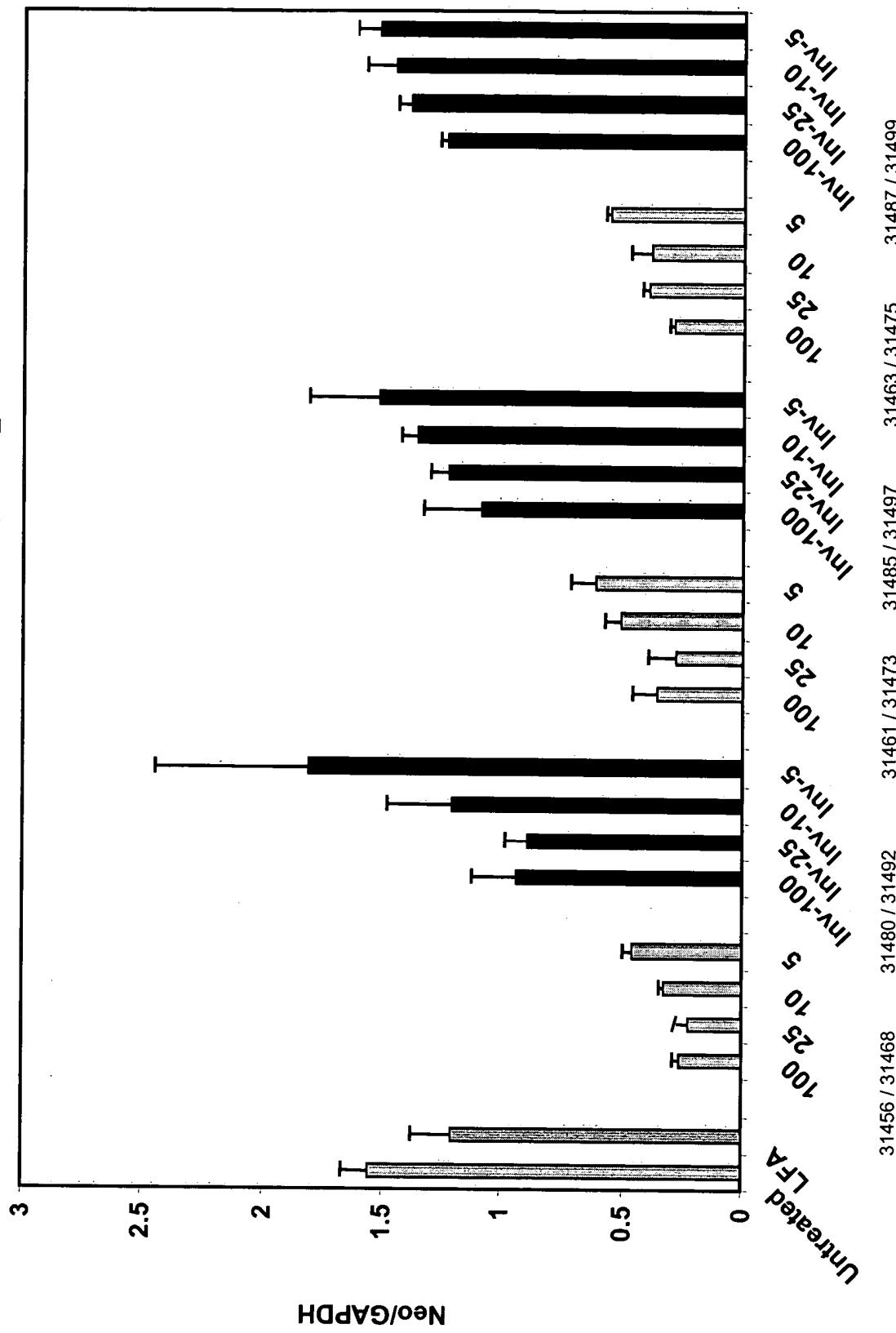


Figure 40: Activity of Stab 7/8 siNA Leads in HCV Subgenomic Replicon

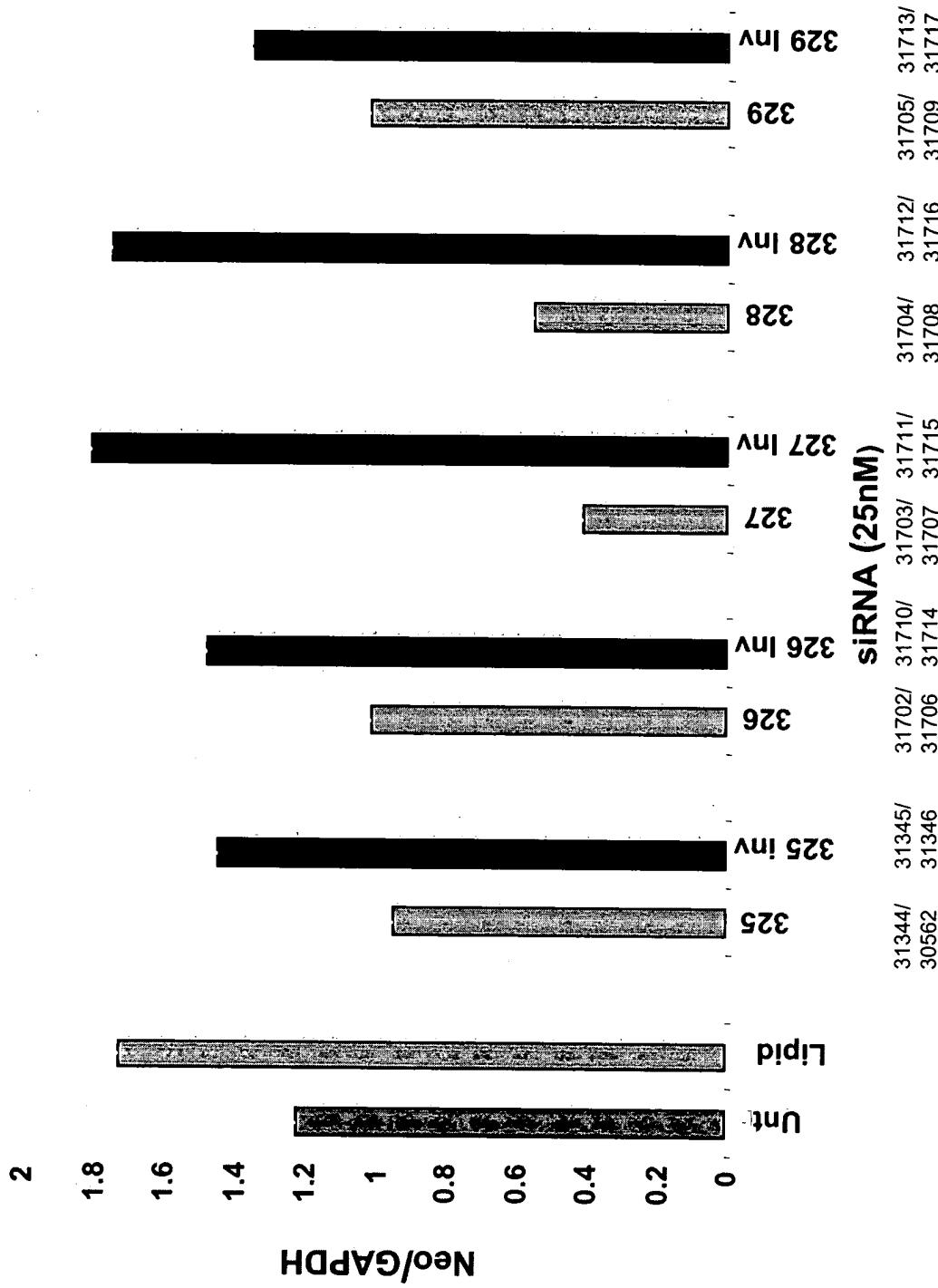
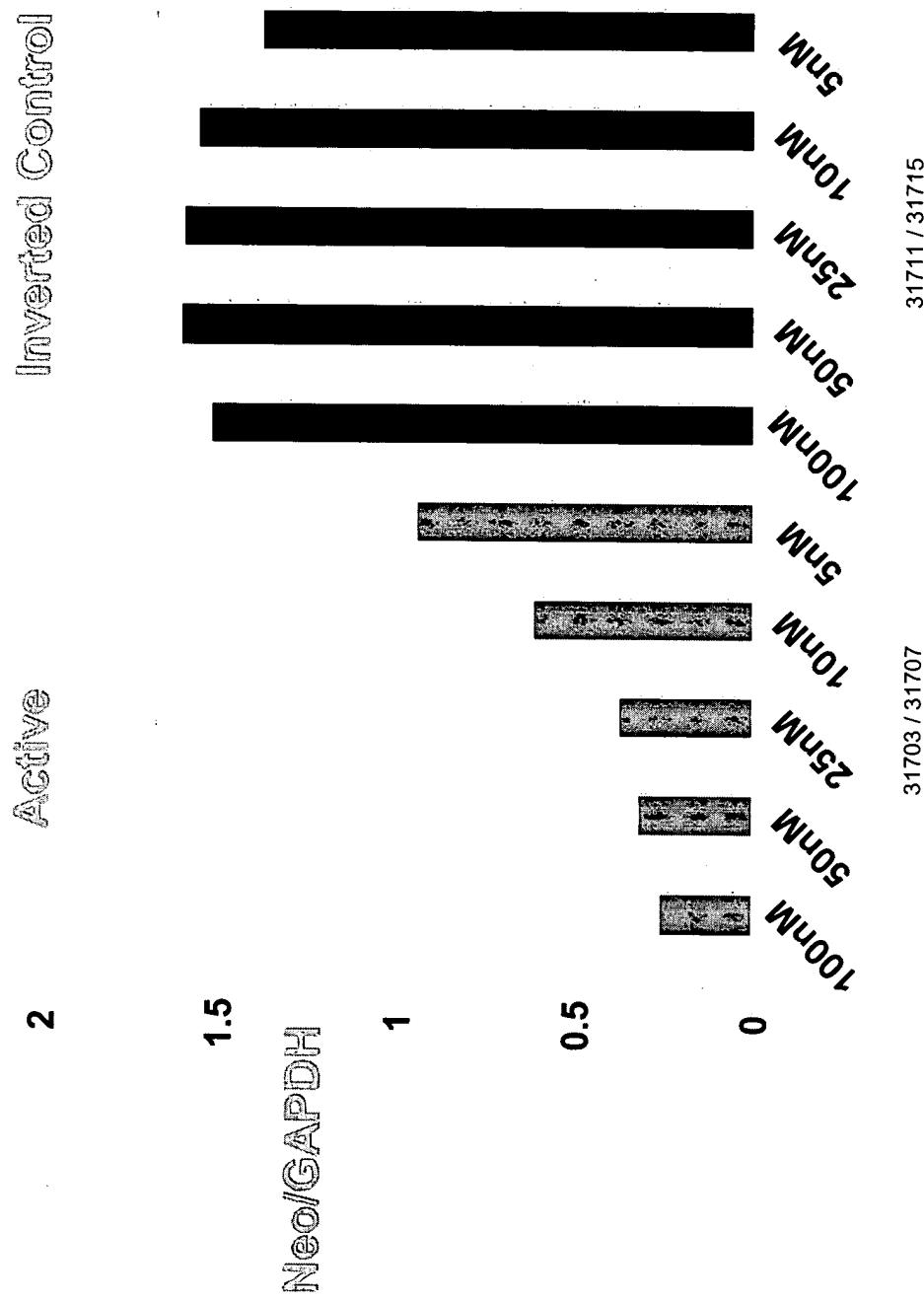


Figure 41: Dose Response with Fully Modified HCV Site 327 siNA



31711 / 31715
31703 / 31707

Figure 42: Solid Phase Post-synthetic conjugation of pteroic acid

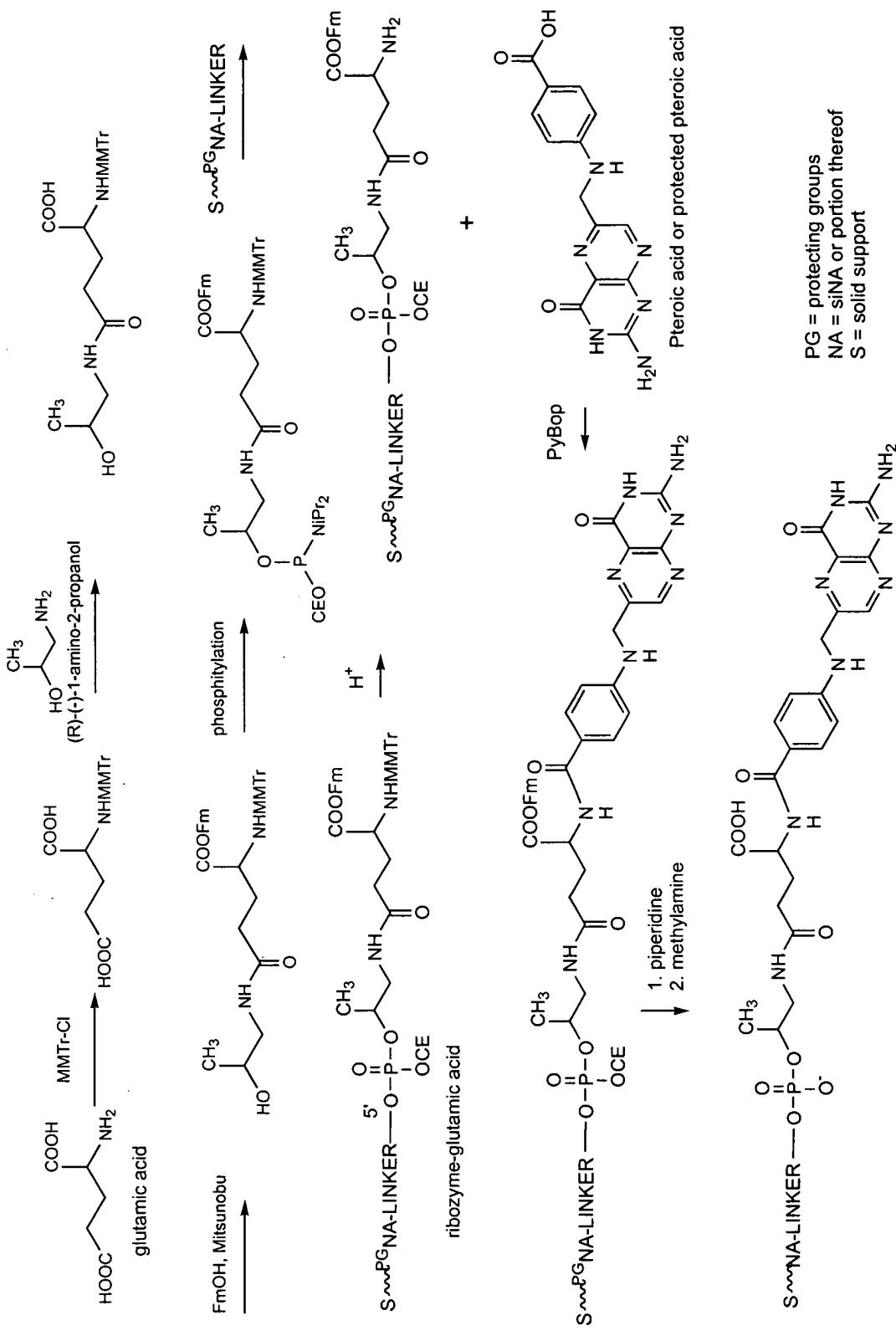
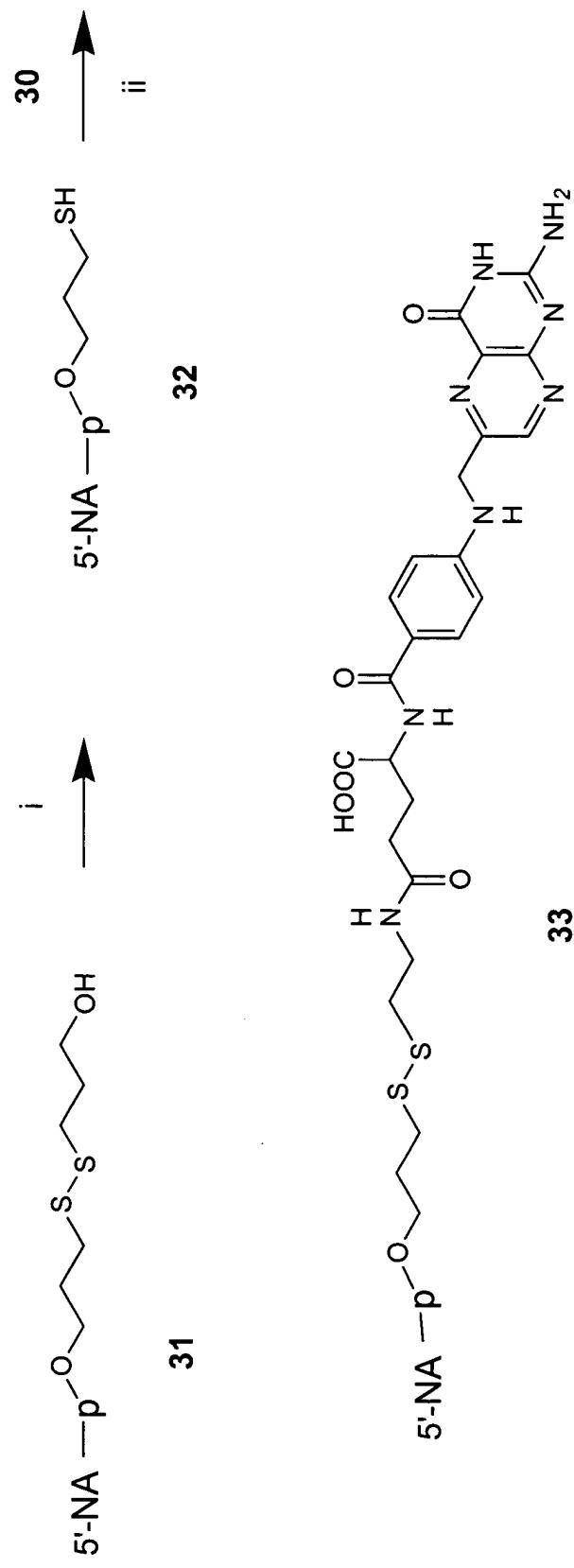


Figure 43



NA = siNA or a portion thereof
p = phosphorous moiety

Figure 44

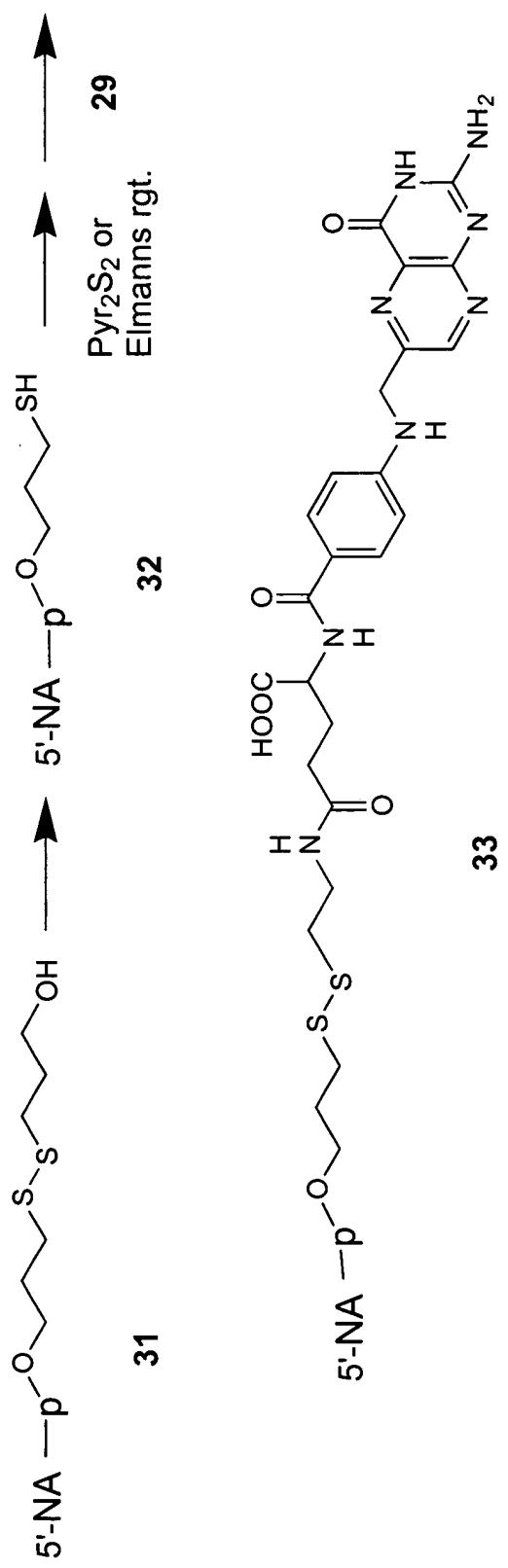


Figure 45: Solid Phase Post-synthetic conjugation of pteroic acid

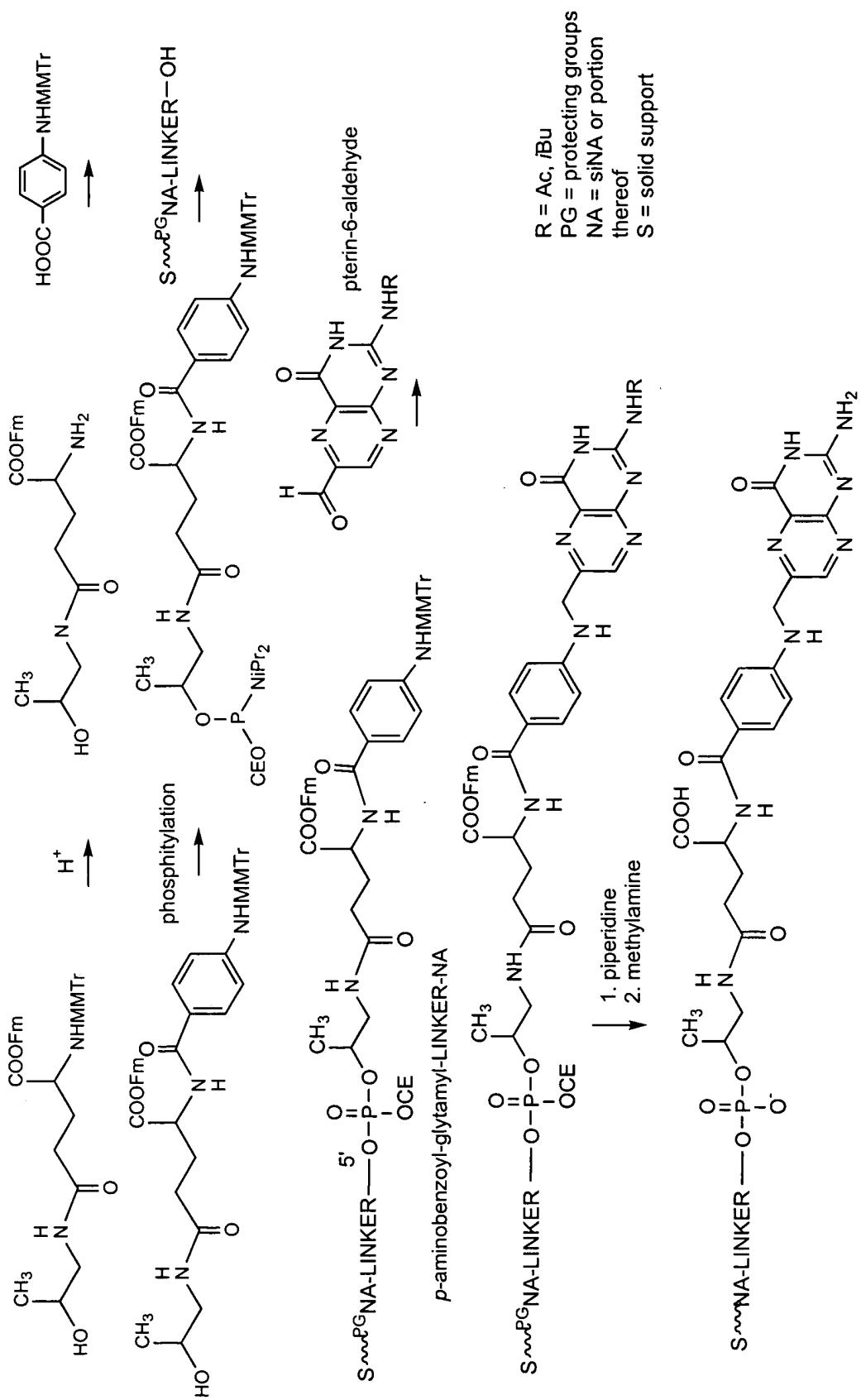


Figure 46: Synthesis of *N*-acetyl-D-galactosamine-2'-aminouridine conjugate

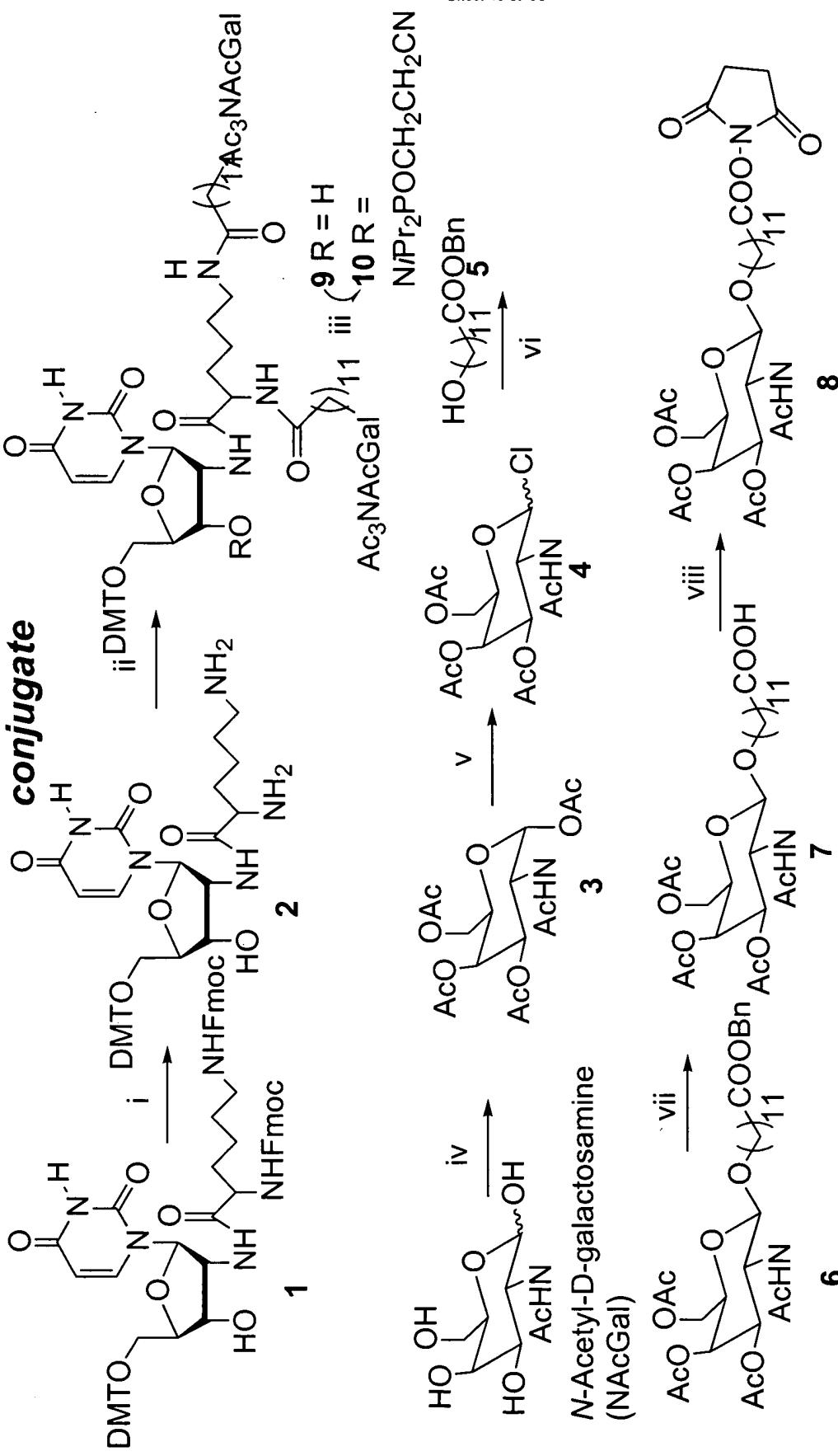
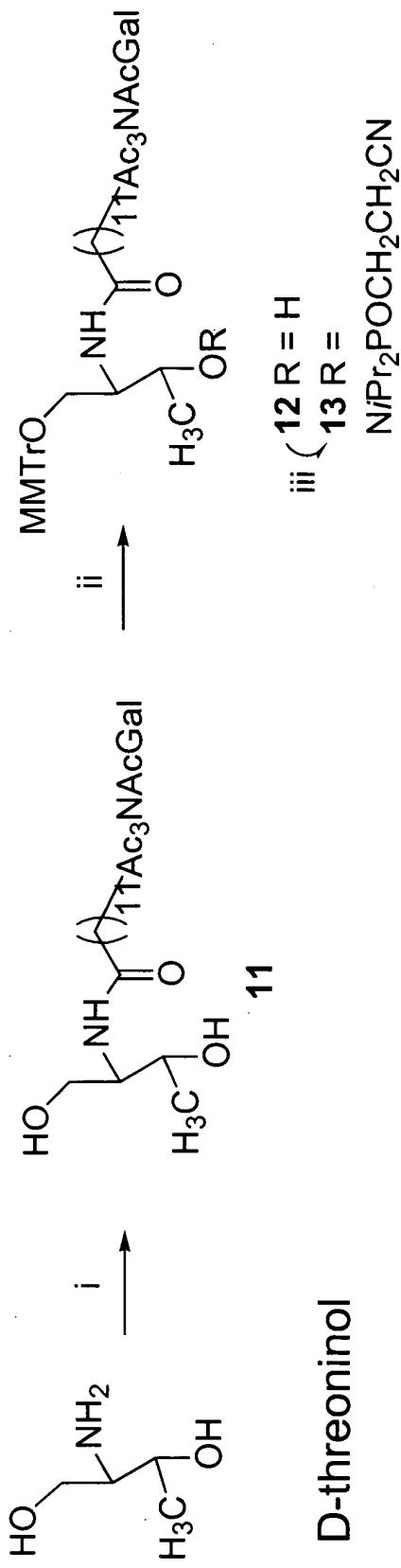
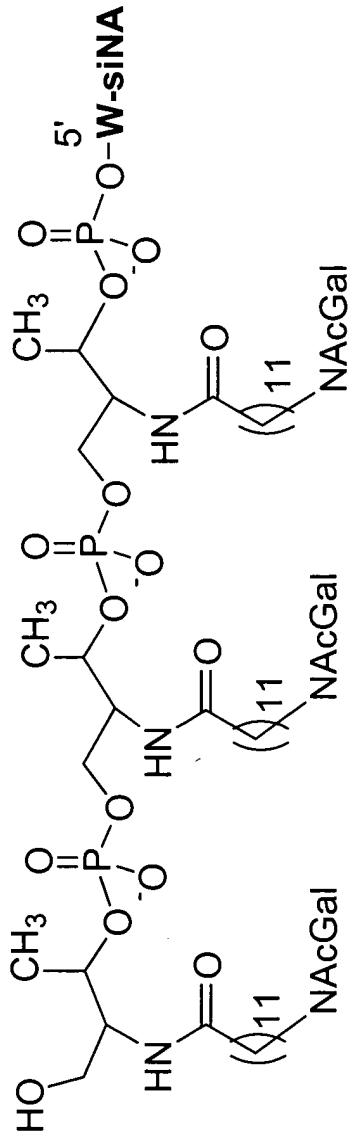


Figure 47: Synthesis of *N*-acetyl-D-galactosamine-D-threoninol conjugate



Reagents and Conditions: (i) 7, DCC, N-hydroxysuccinimide, (ii) MMTr-Cl, pyridine, (iii) 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite, 1-methylimidazole, DIPEA, CH₂Cl₂.

Figure 48: Conjugation of targeting ligands to the 5'-end of a siNA molecule



N-acetyl-D-galactosamine conjugate

Figure 49: *Synthesis of dodecanoic acid linker*

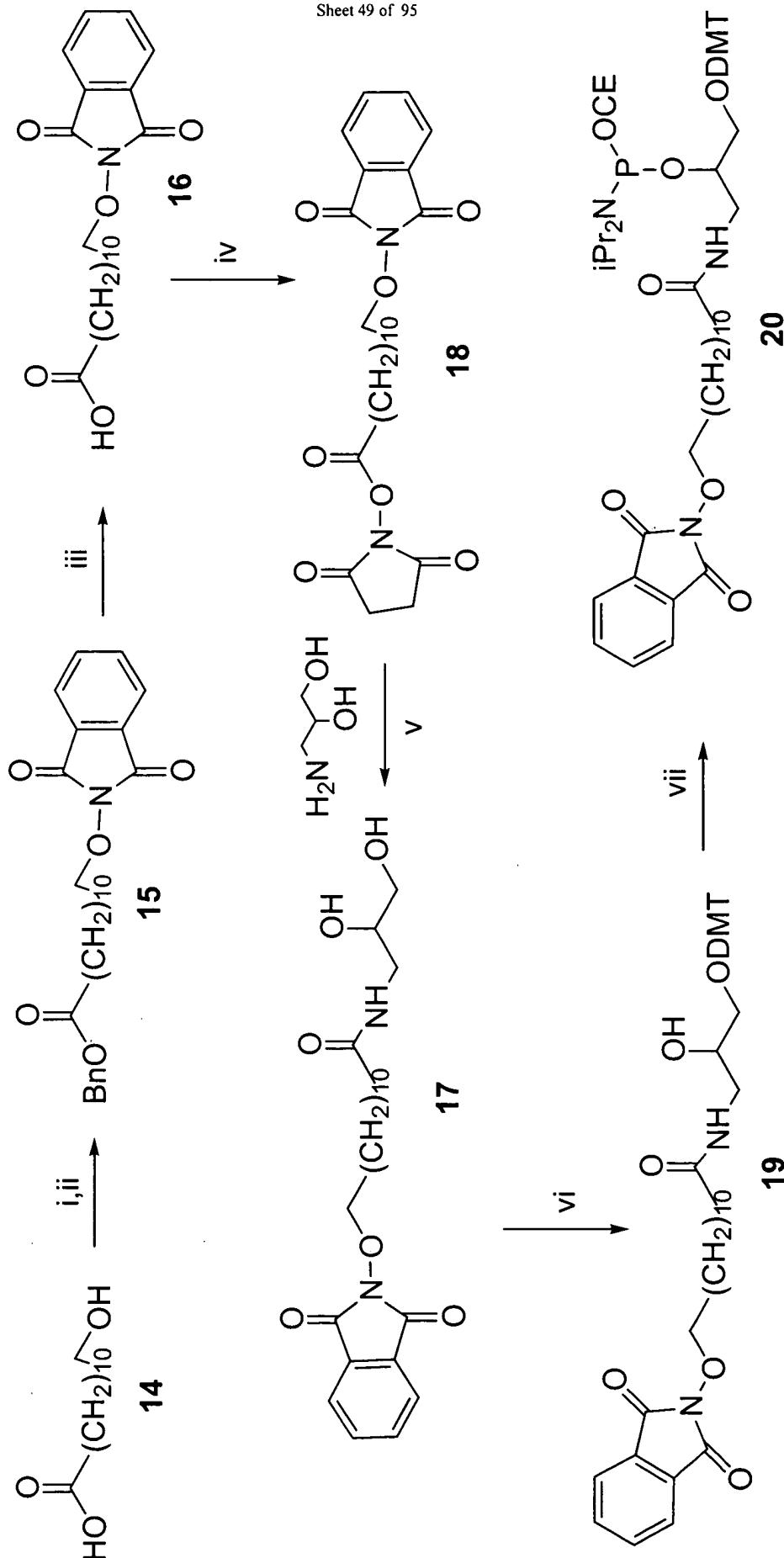


Figure 50: Oxime linked siNA/Peptide Conjugate

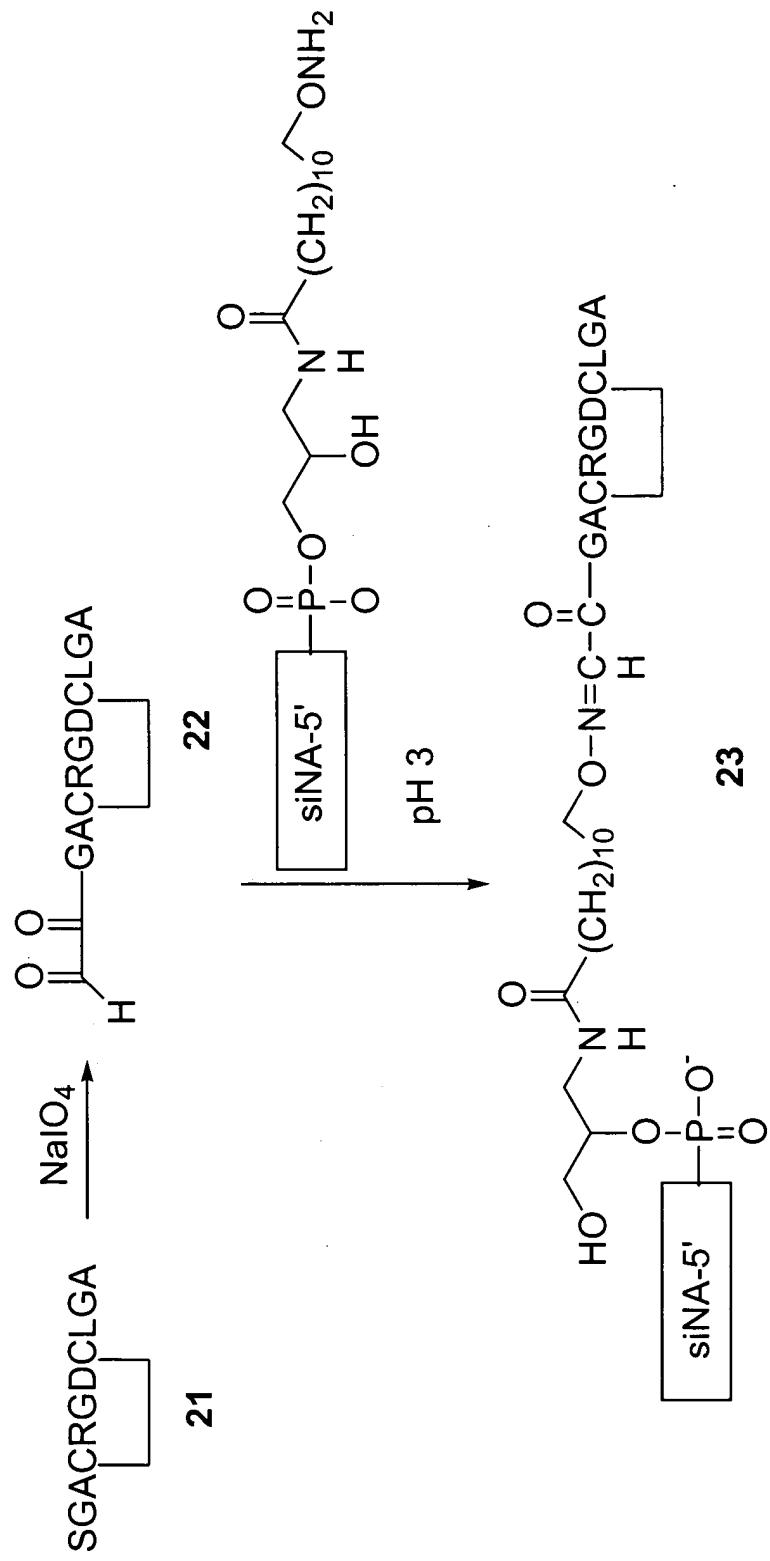
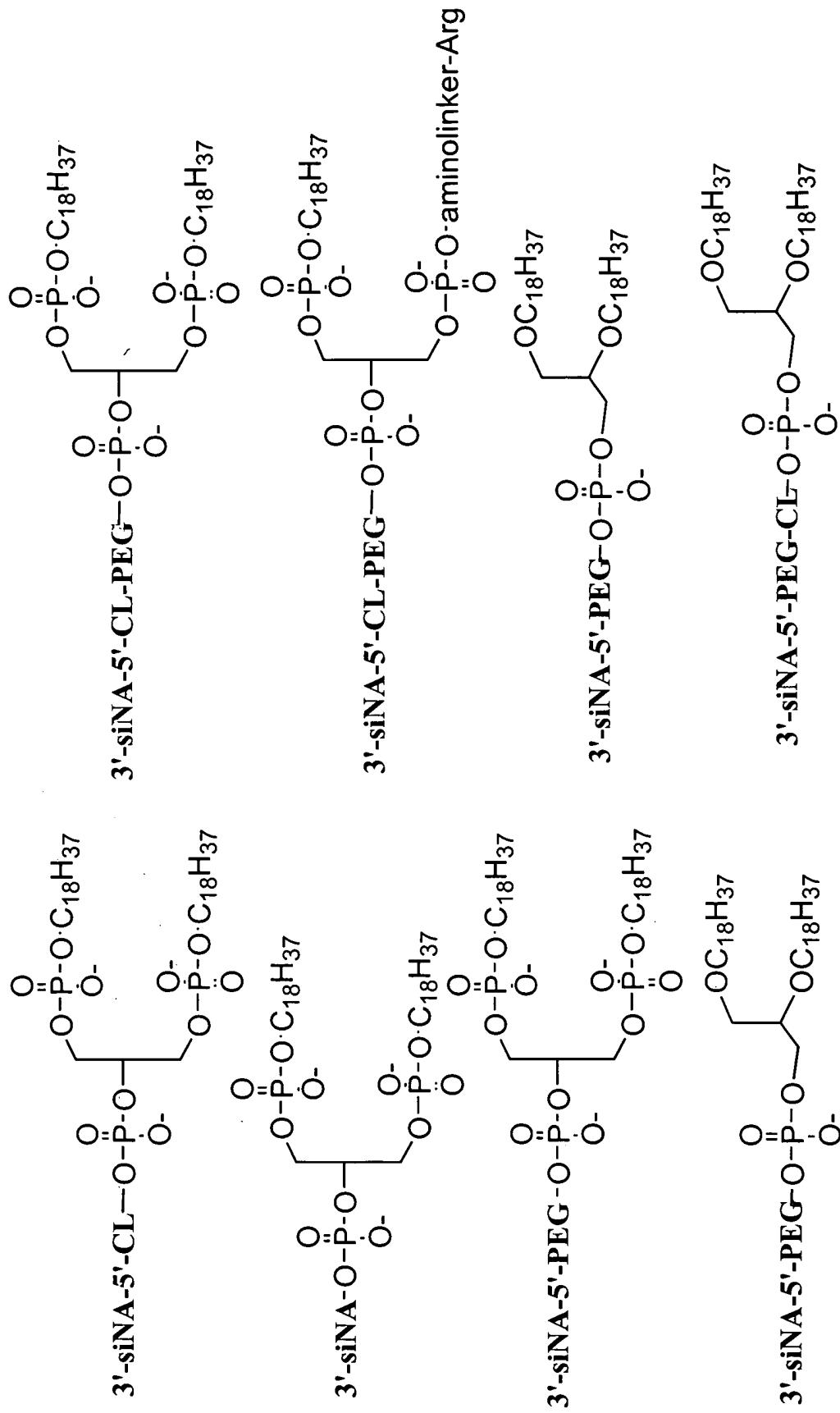


Figure 51: siNA/Phospholipid Conjugates



PEG=polyethylene glycol

CL=cleavable linker (e.g. A-dT, C-dT)

siNA= short interfering nucleic acid molecule or a portion thereof

Figure 52: siNA Phospholipid Conjugate

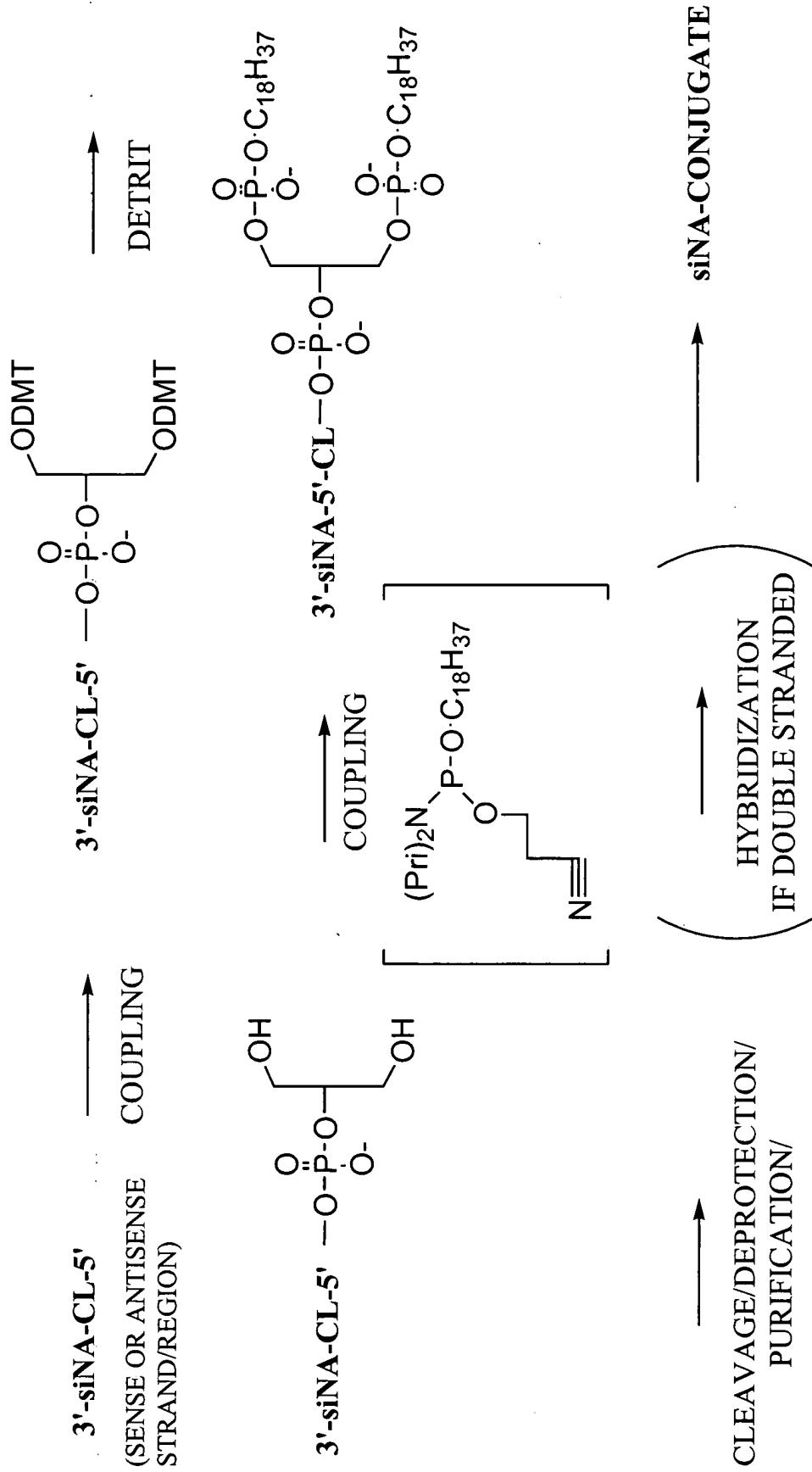
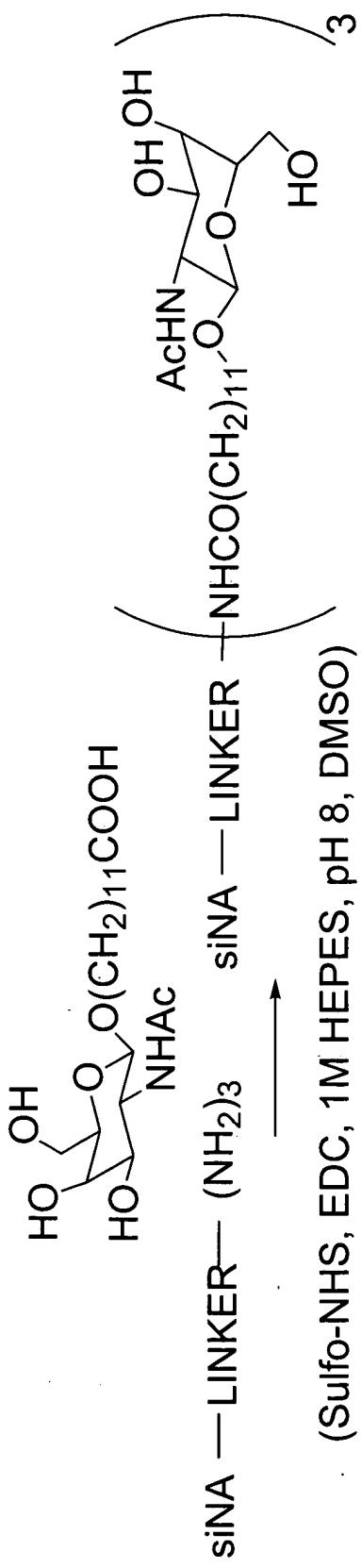
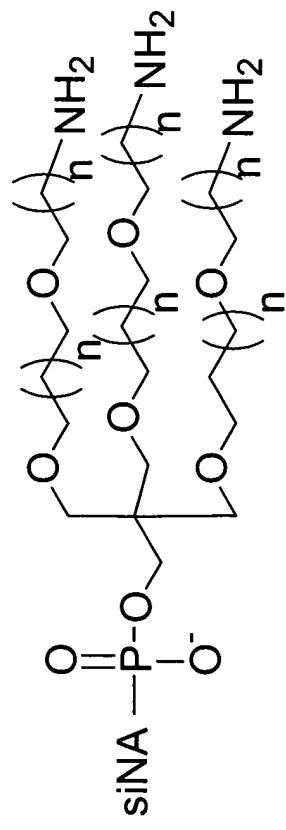


Figure 53: siNA-NAcGalactosamine post-synthetic coupling



FOR EXAMPLE: OLIGO-LINKER =



Where n is an integer from 1 to 20

Figure 54: siNA Cholesterol Conjugate

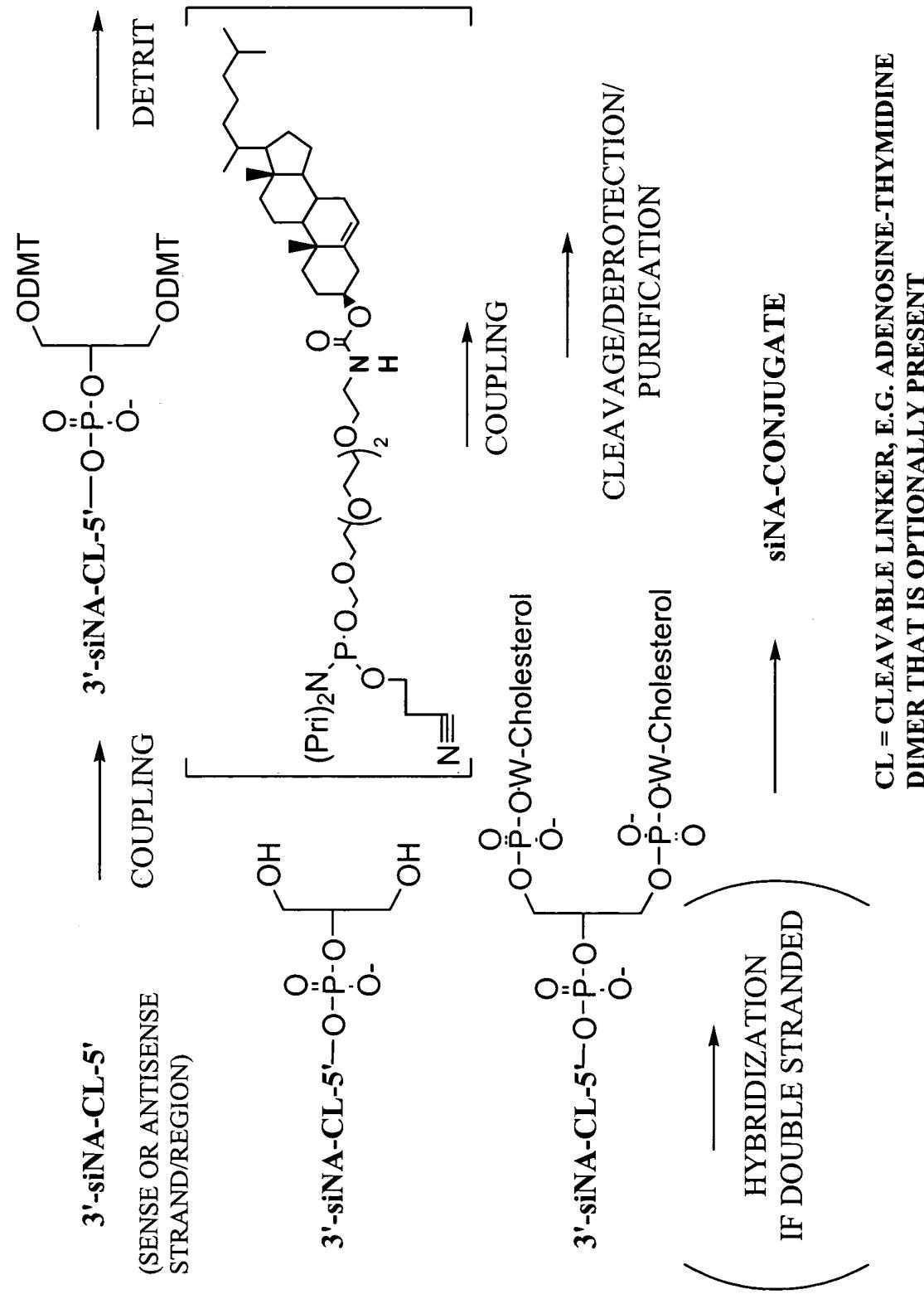


Figure 55: siNA 3'-PEG Conjugate

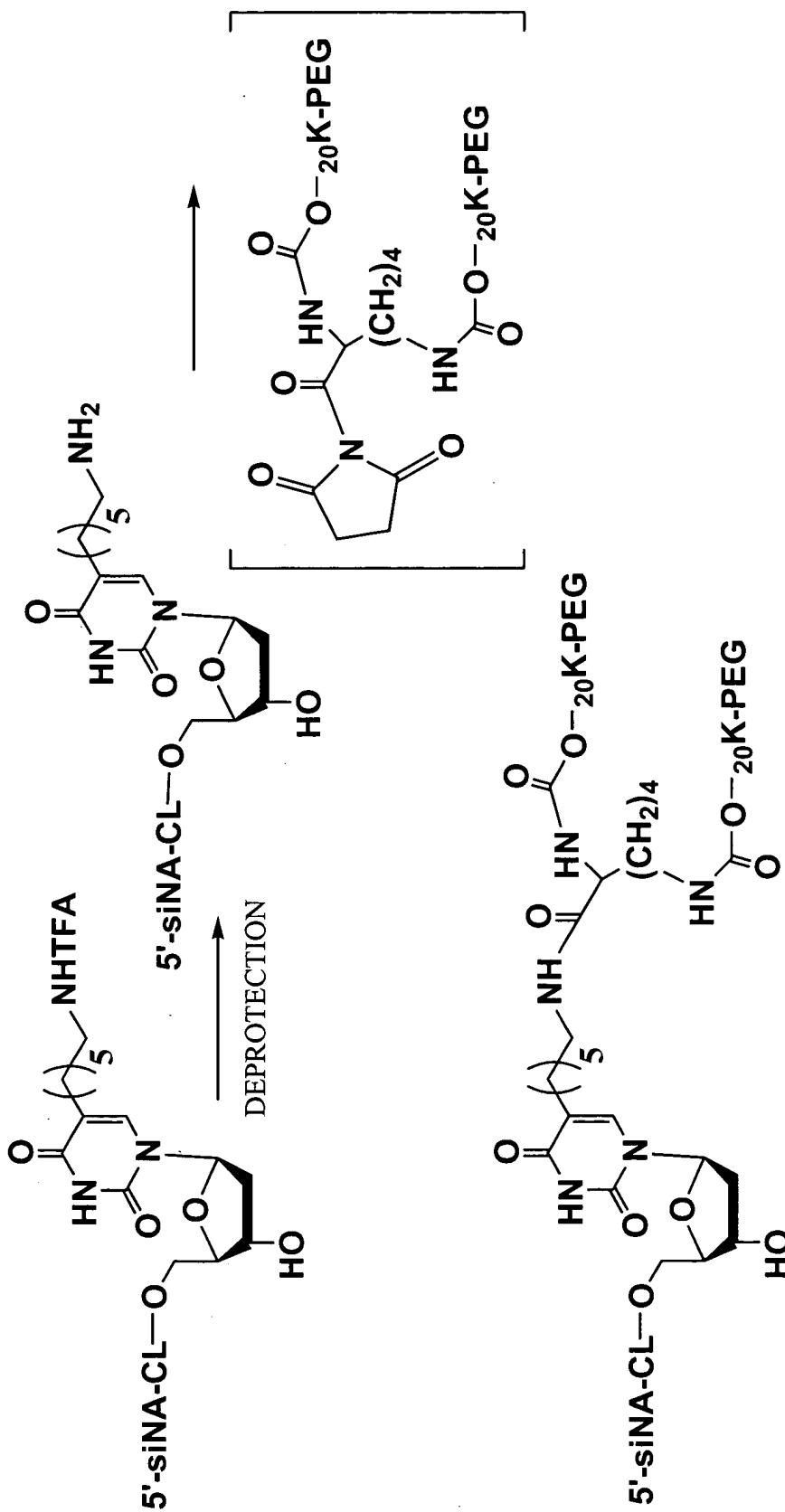


Figure 56: siNA 3'-Cholesterol Conjugate

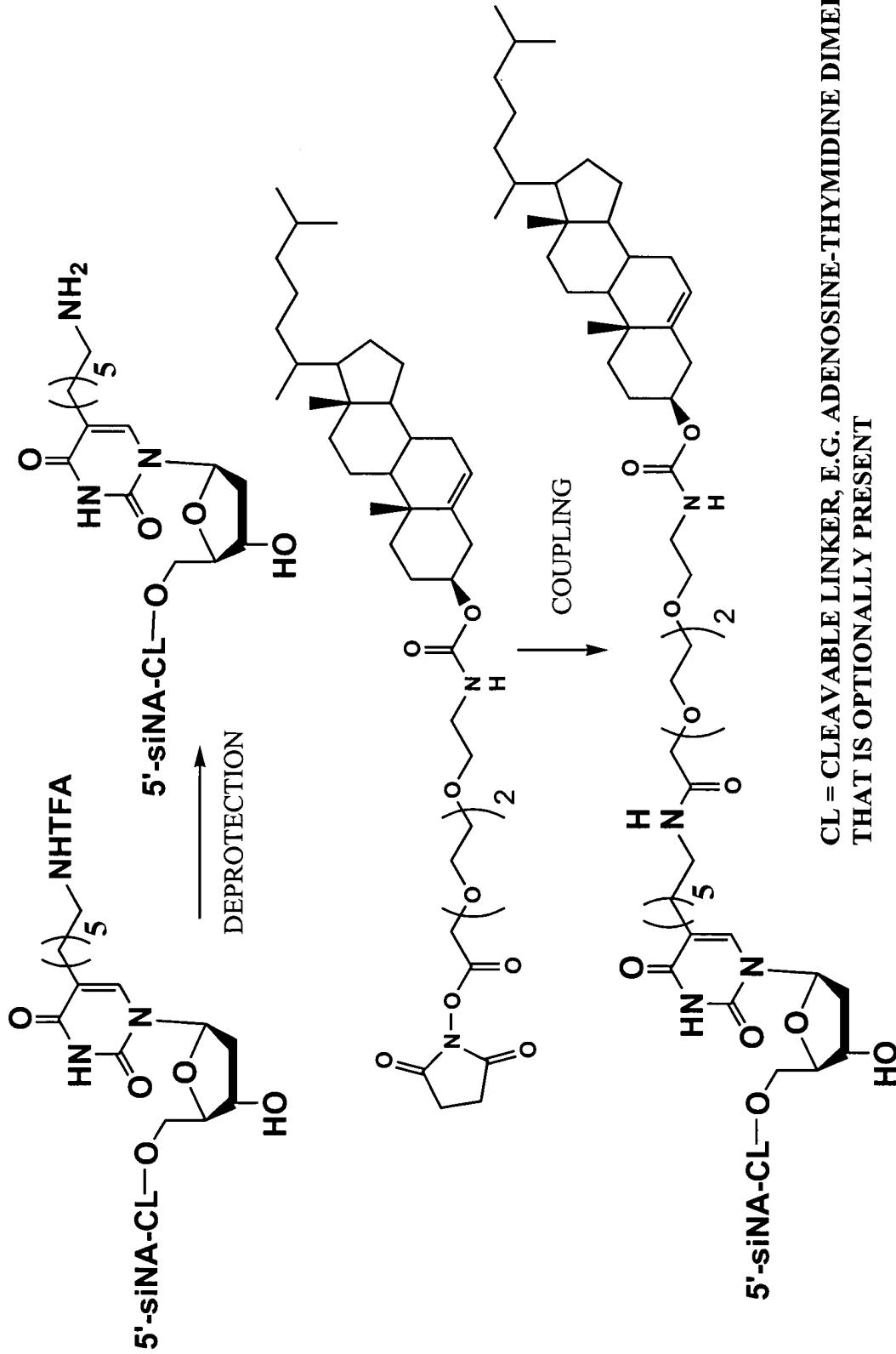
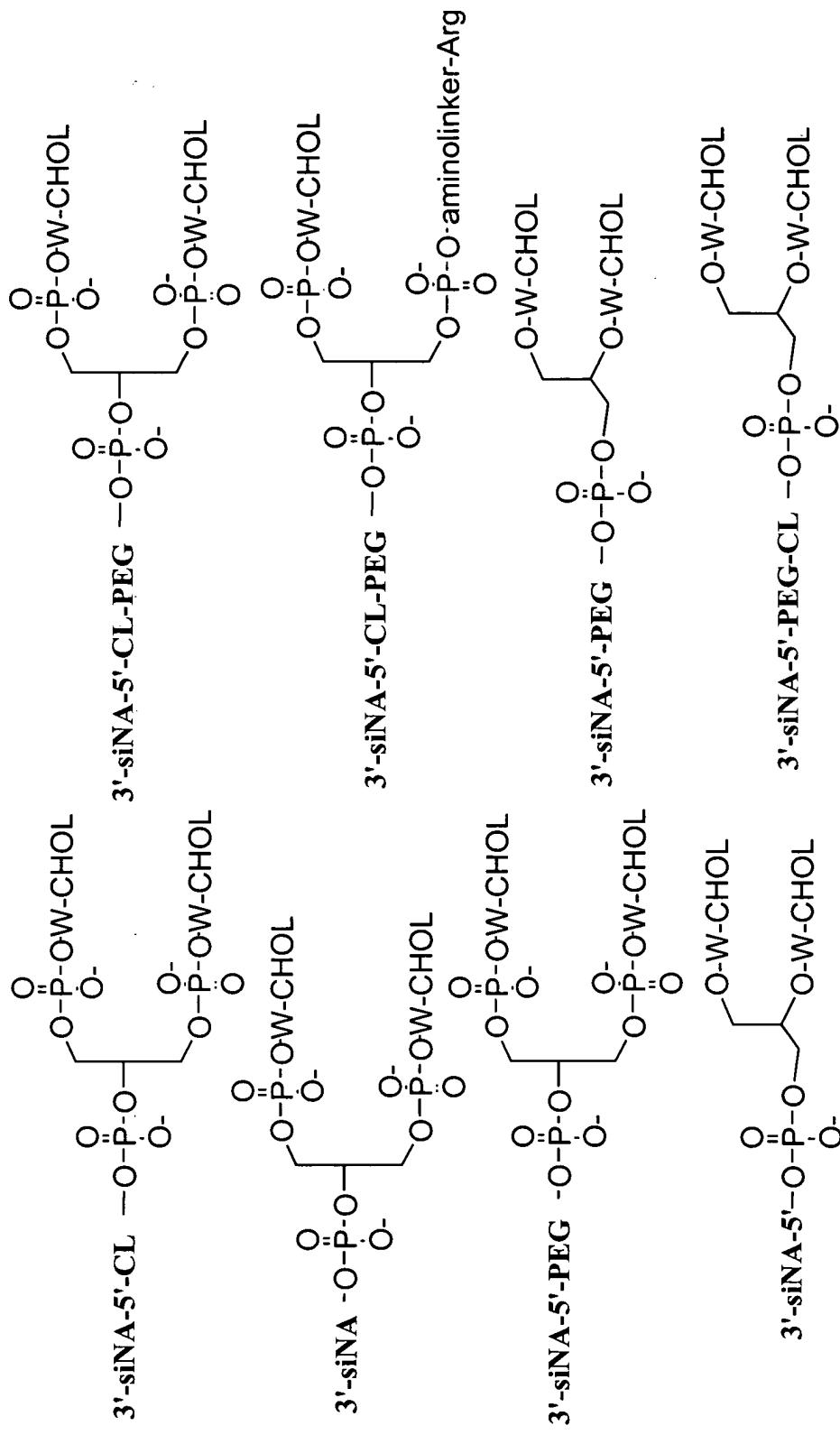
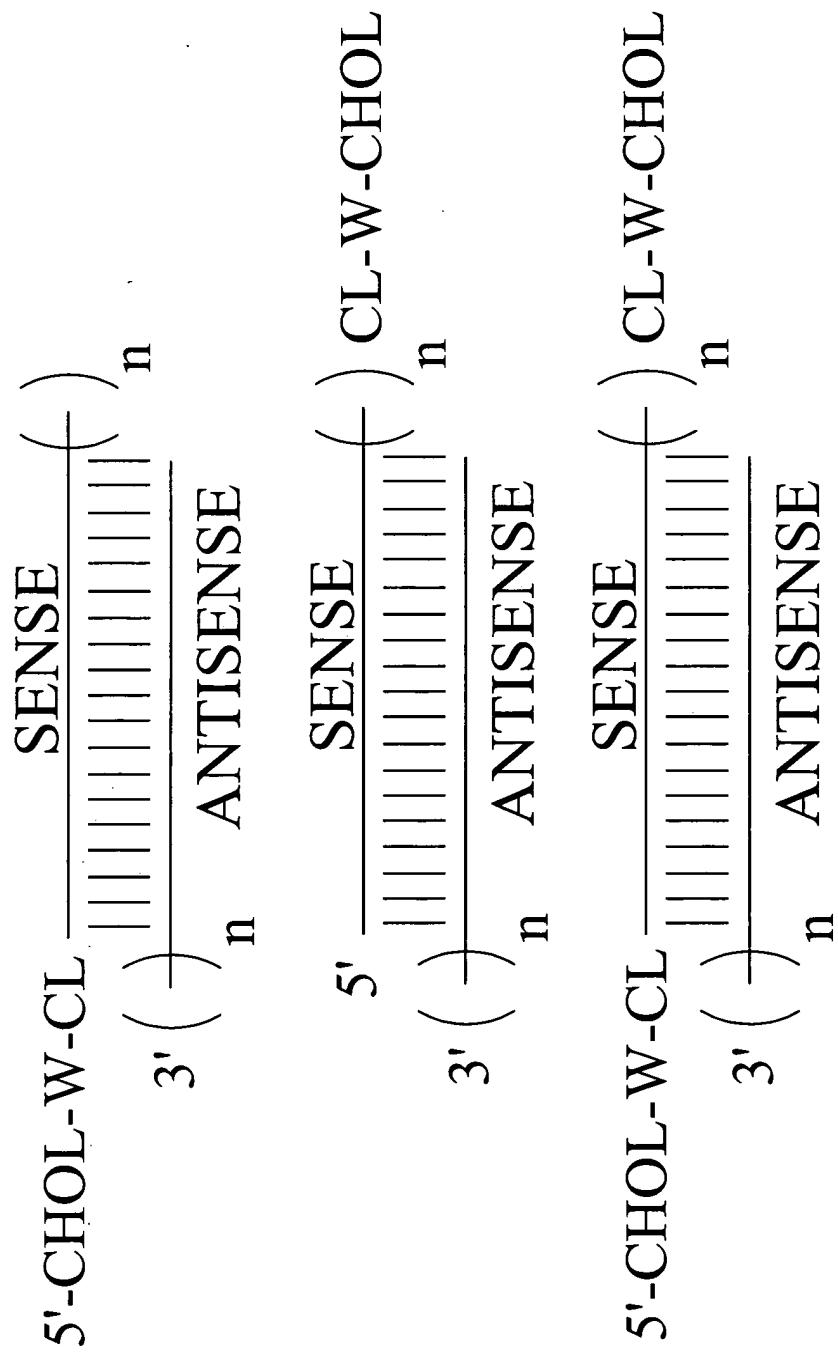


Figure 57: Nucleic Acid Cholesterol Conjugates



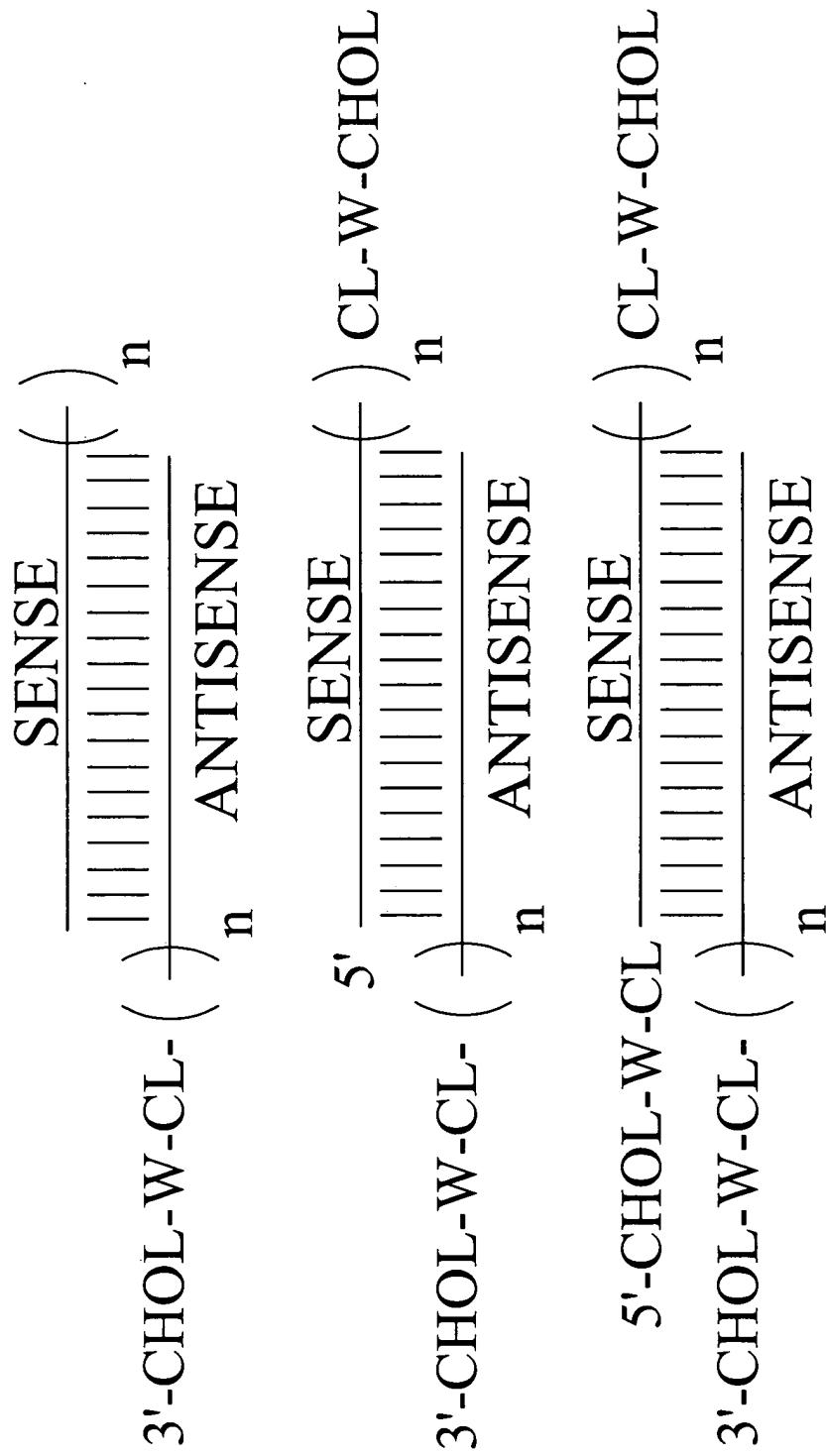
PEG=polyethylene glycol
CL=cleavable linker (e.g. A-dT, C-dT)
siNA= short interfering nucleic acid molecule or a portion thereof
CHOL=cholesterol or an analog or metabolite thereof
W= linker molecule (see for example Formulae 109 or 112)

Figure 58: siNA Cholesterol Conjugates

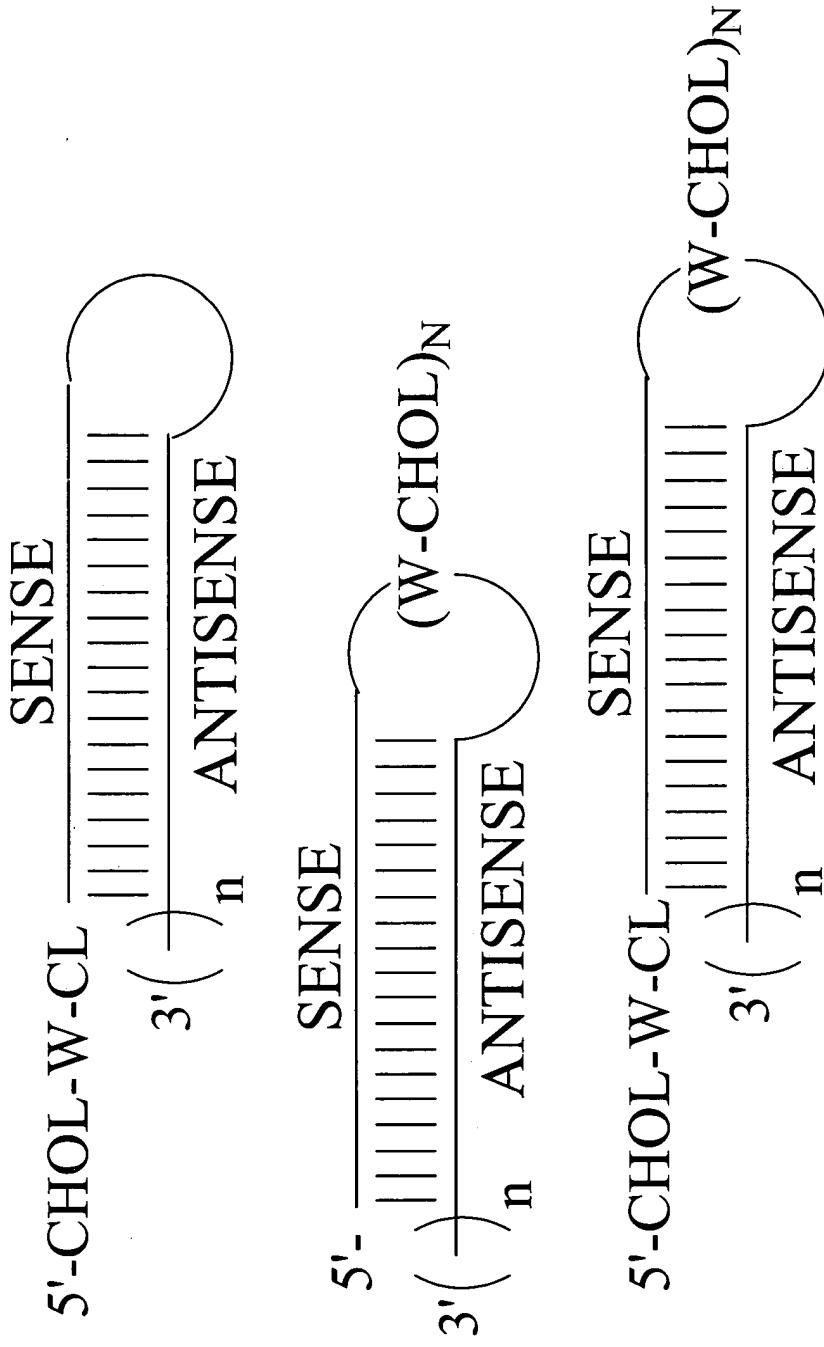


CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
 CHOL=cholesterol or an analog or metabolite thereof
 W=linker molecule (see for example Formulae 107, 108, 109 or 115)
 n = integer, e.g. 1, 2, or 3

Figure 59: siNA Cholesterol Conjugates



CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
CHOL=cholesterol or an analog or metabolite thereof
W=linker molecule (see for example Formulae 107, 108, 109 or 115)
n = integer, e.g. 1, 2, or 3

Figure 60: siNA Cholesterol Conjugates

CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present

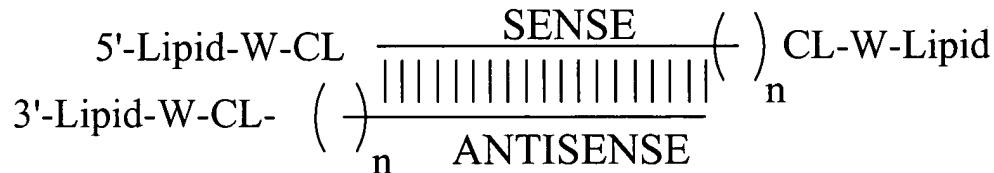
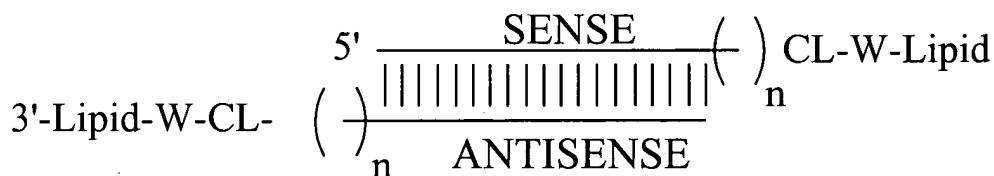
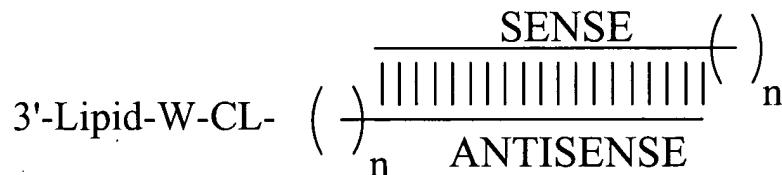
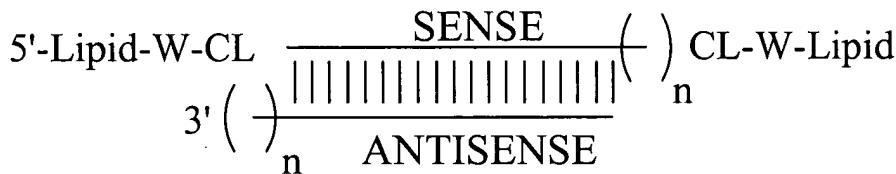
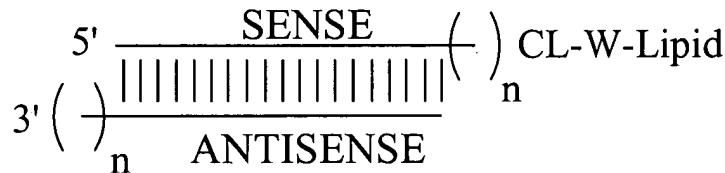
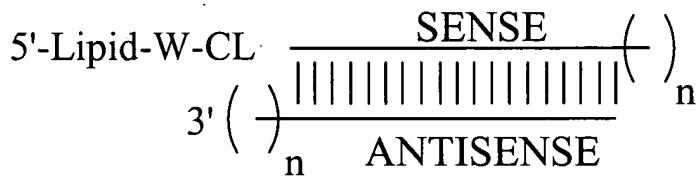
CHOL=cholesterol or an analog or metabolite thereof

W=linker molecule (see for example Formulae 107, 108, 109 or 112)

n = integer, e.g. 1, 2, or 3

N=integer, e.g. 1, 2, 3, or 4

Figure 61: siNA Lipid Conjugates



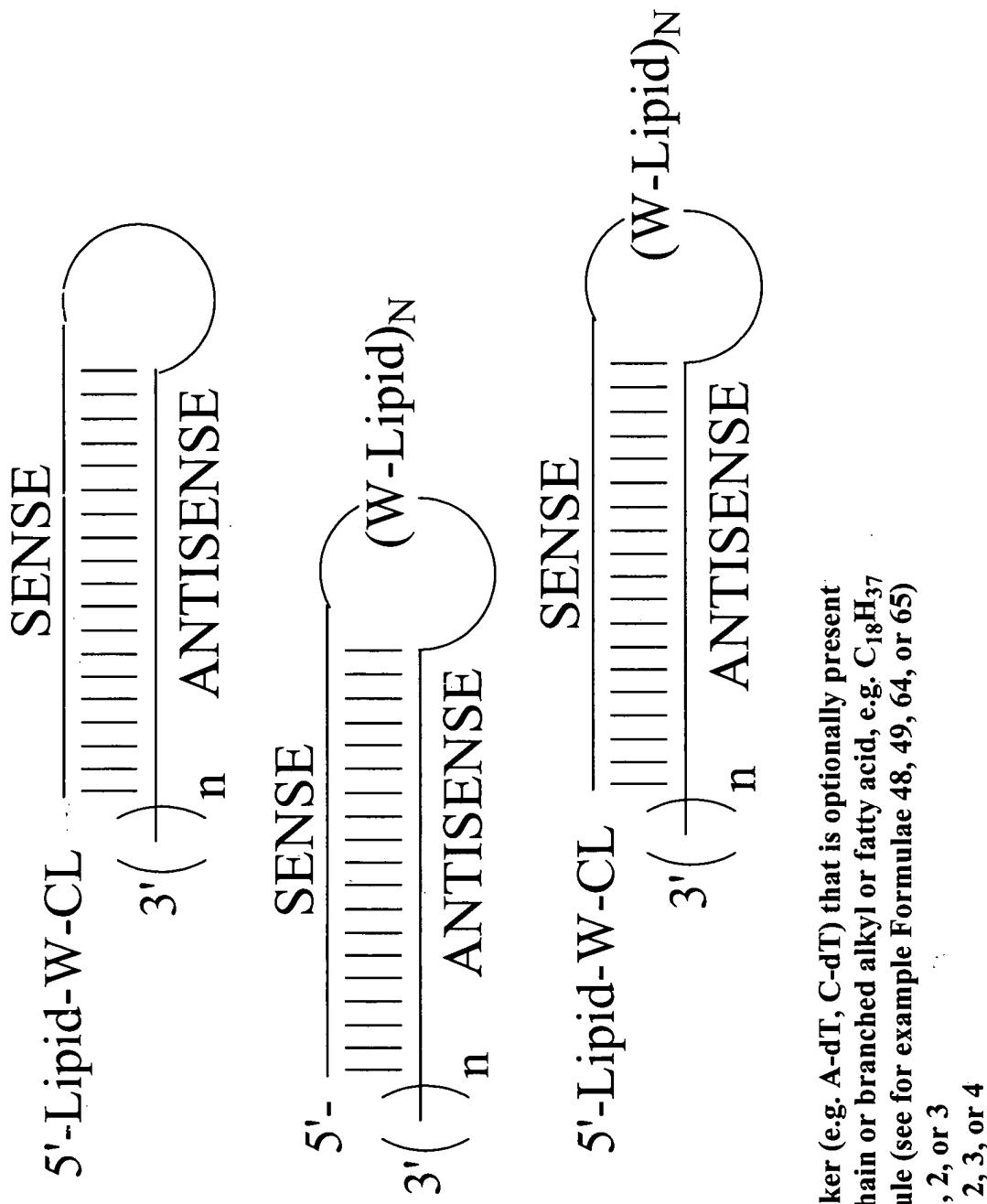
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present

Lipid=Straight chain or branched alkyl or fatty acid, e.g. C₁₈H₃₇

W=linker molecule (see for example Formulae 48, 49, 64, or 65)

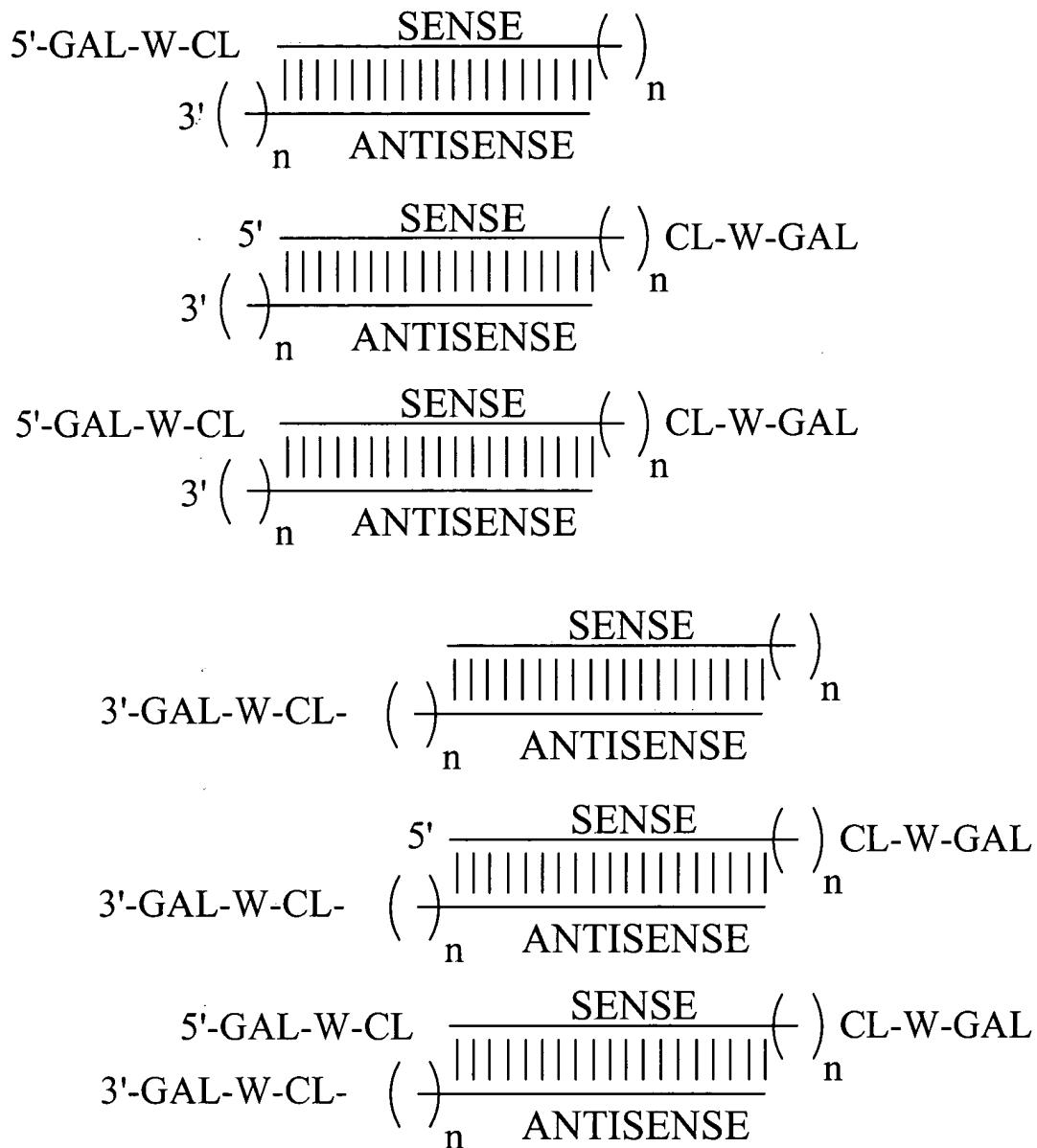
n = integer, e.g. 1, 2, or 3

Figure 62: siNA Lipid Conjugates



CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
Lipid=Straight chain or branched alkyl or fatty acid, e.g. C₁₈H₃₇
W=linker molecule (see for example Formulae 48, 49, 64, or 65)
 n =integer, e.g. 1, 2, or 3
 N =integer, e.g. 1, 2, 3, or 4

Figure 63: siNA Galactosamine Conjugates



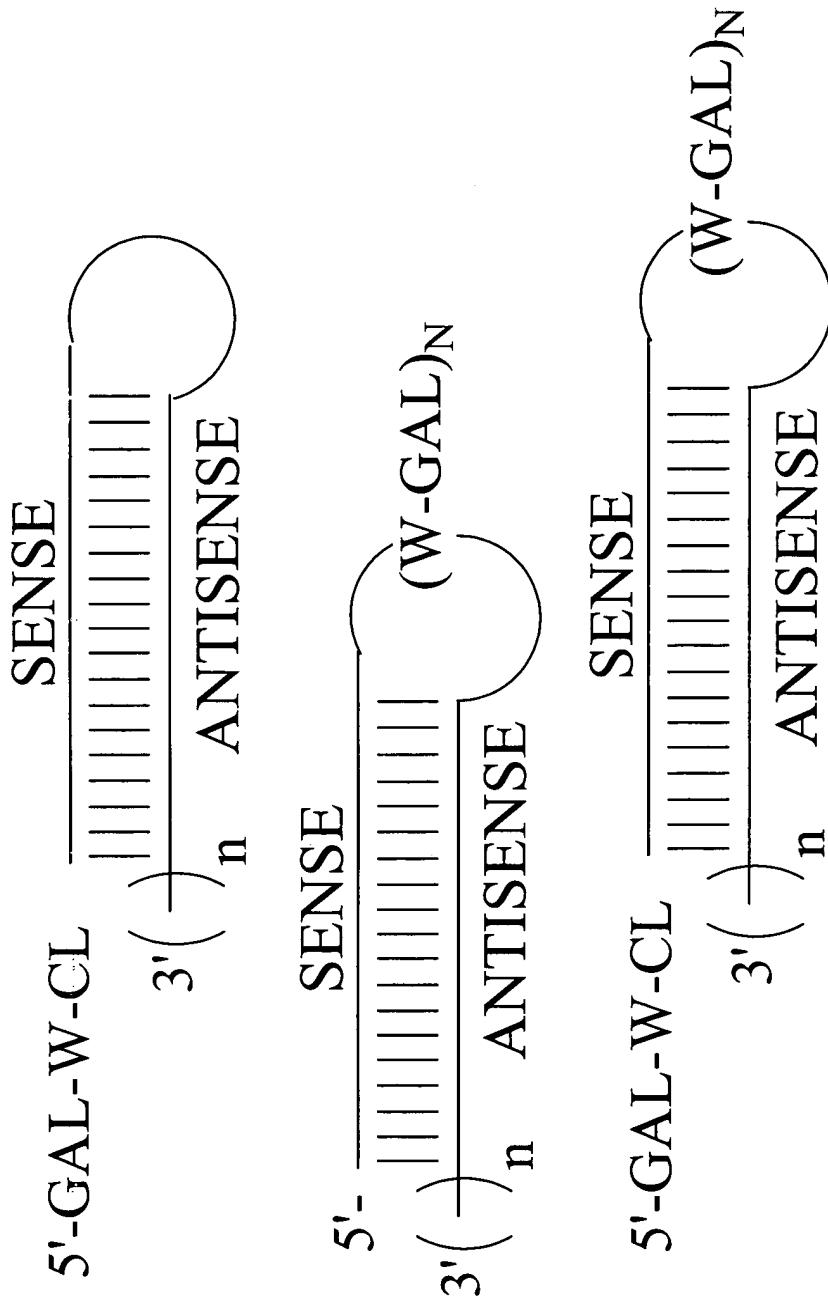
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present

GAL=GALACTOSAMINE; e.g. compounds having Formulae 51-56, 86, 92, 99, 100, 103, 105, 106

W= linker molecule (see for example Formulae 102 or 103)

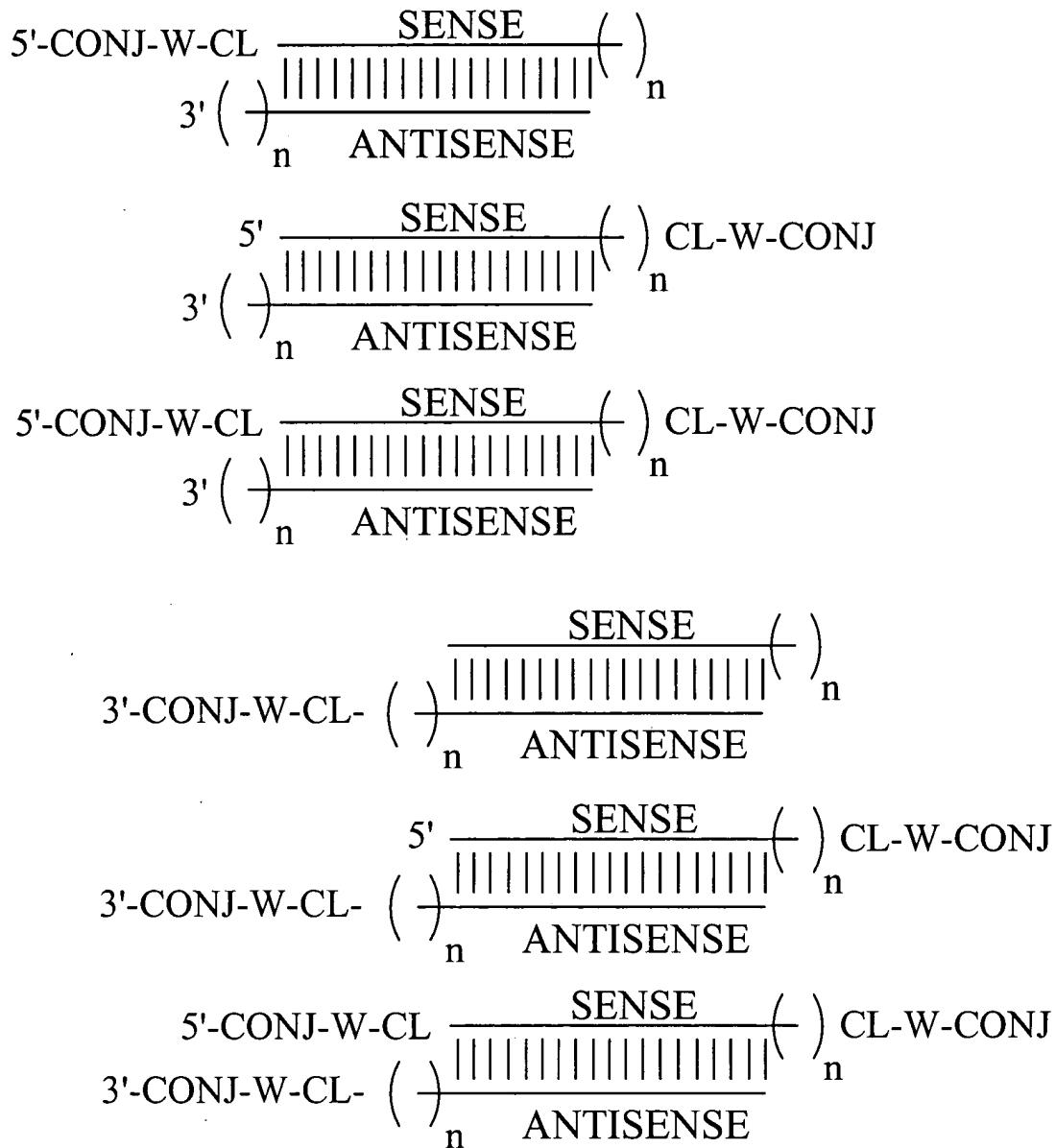
n = integer, e.g. 1, 2, or 3

Figure 64: siNA Galactosamine Conjugates

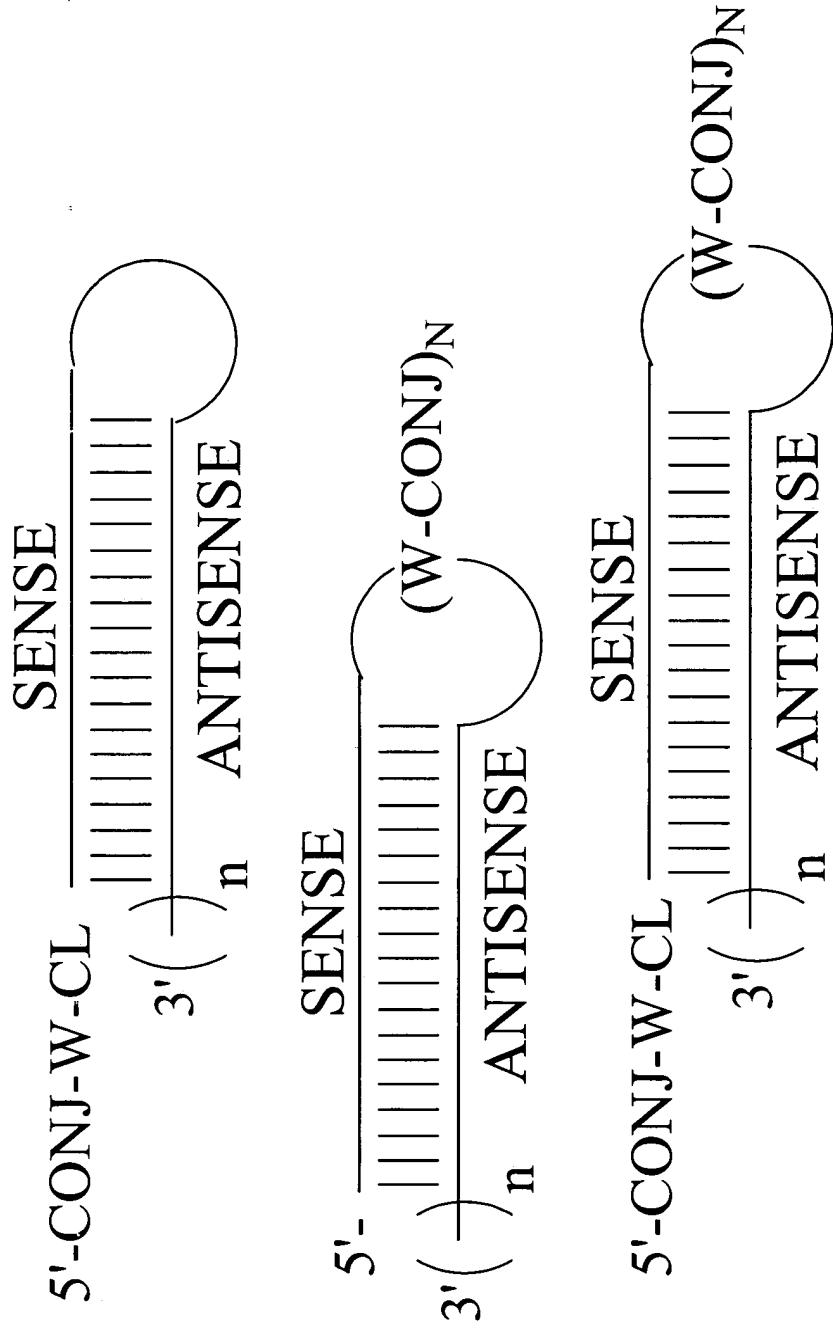


CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
GAL=GALACTOSAMINE; e.g. compounds having Formulae 51-56, 86, 92, 99, 100, 103, 105, 106
W=linker molecule (see for example Formulae 102 or 103)
 n =integer, e.g. 1, 2, or 3
 N =integer, e.g. 1, 2, 3, or 4

Figure 65: Generalized siNA Conjugate Design



CONJ=any biologically active molecule or conjugate as described herein
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
W=linker molecule
n=integer, e.g. 1, 2, or 3

Figure 66: Generalized siNA Conjugate design

CONJ=any biologically active molecule or conjugate as described herein

CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present

W=linker molecule

n = integer, e.g. 1, 2, or 3

N=integer, e.g. 1, 2, 3, or 4

Figure 67: Distribution of Intact siNA in Liver After SC Administration of Conjugated or Unconjugated Chemistries

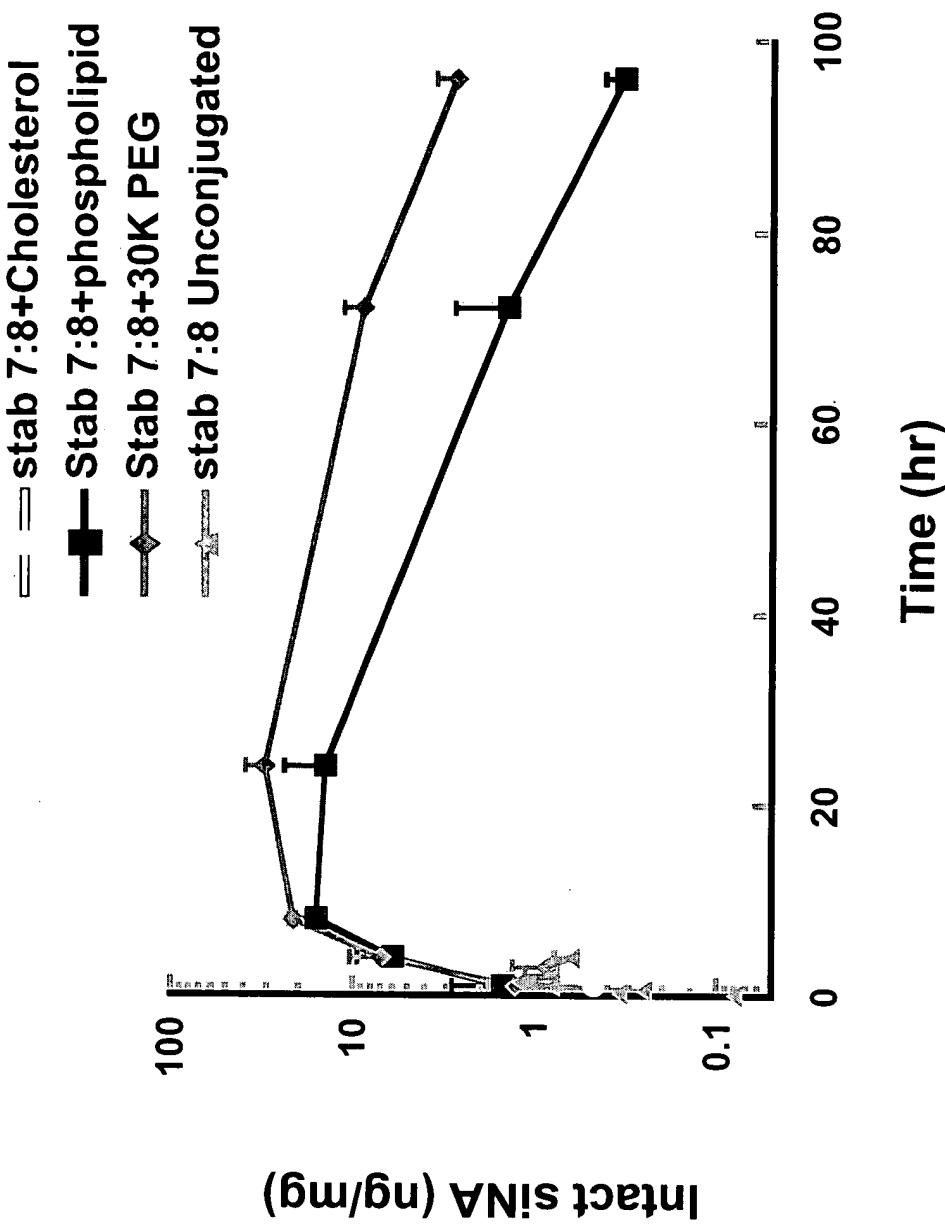


Figure 68: Lipid Free Delivery of HBV siNA Conjugates in Cell Culture

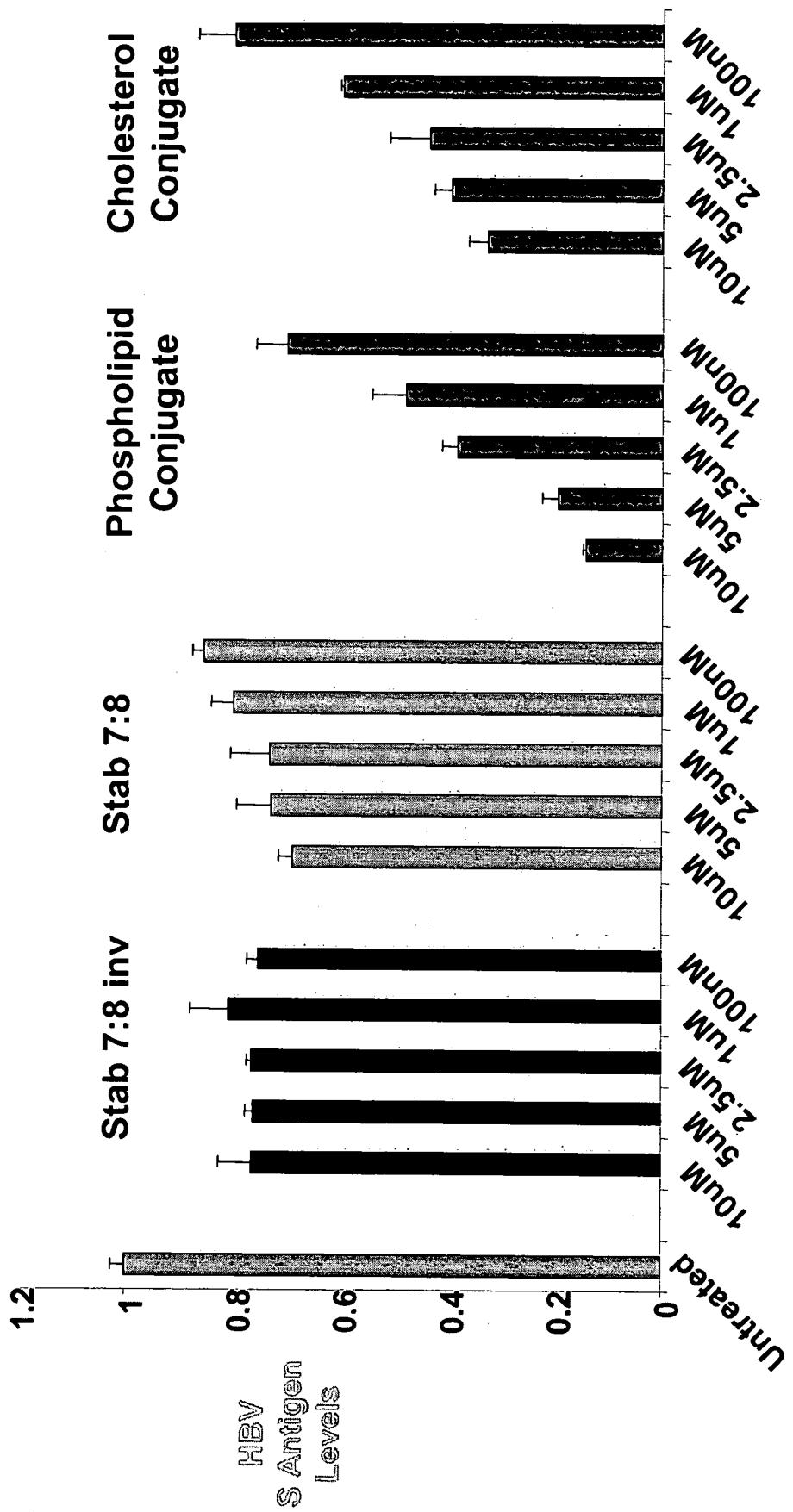


Figure 69: Scale-up of “mono” Galactosamine phosphoramidite

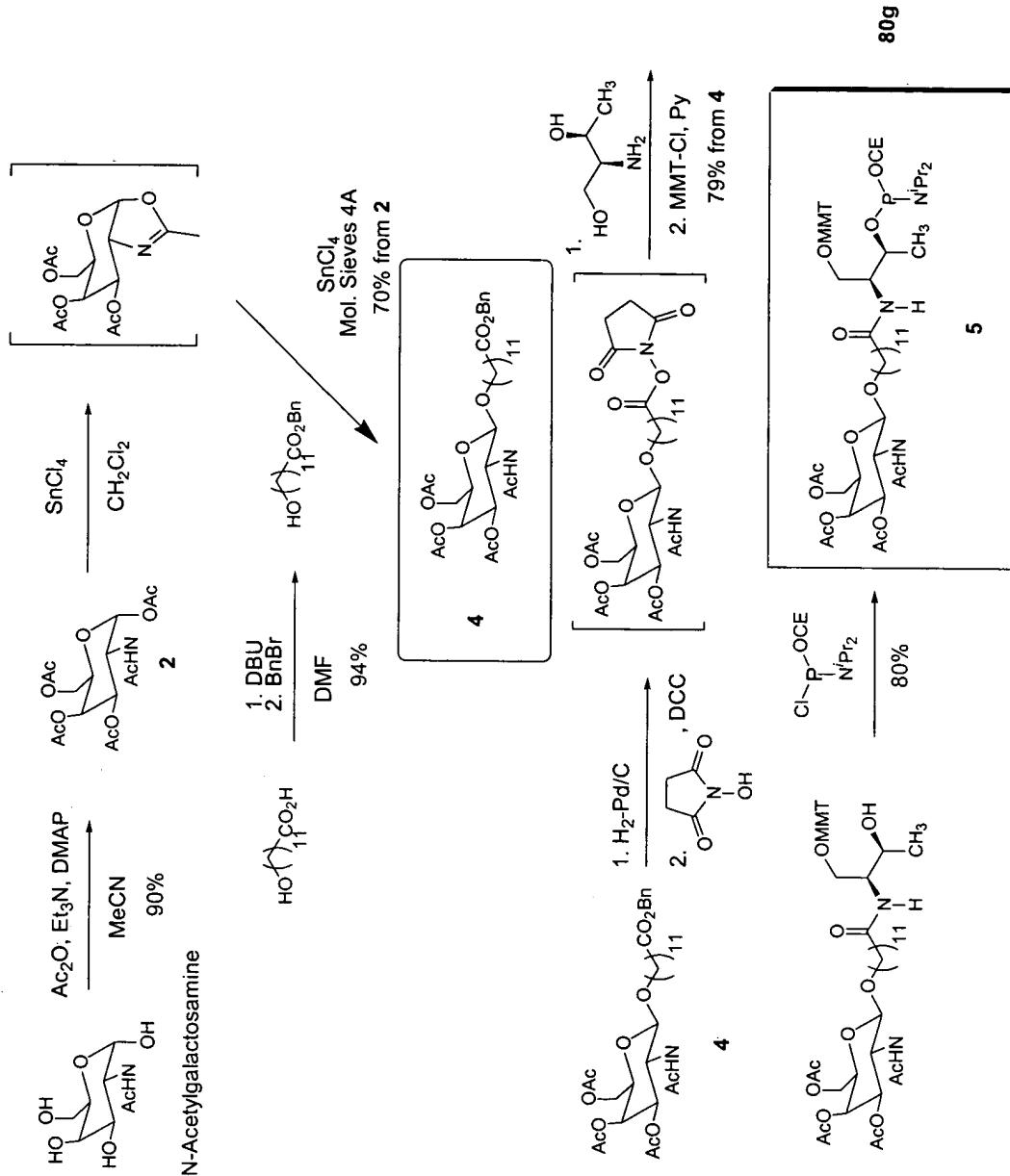


Figure 70: Synthesis of “tri” Galactosamine phosphoramidite

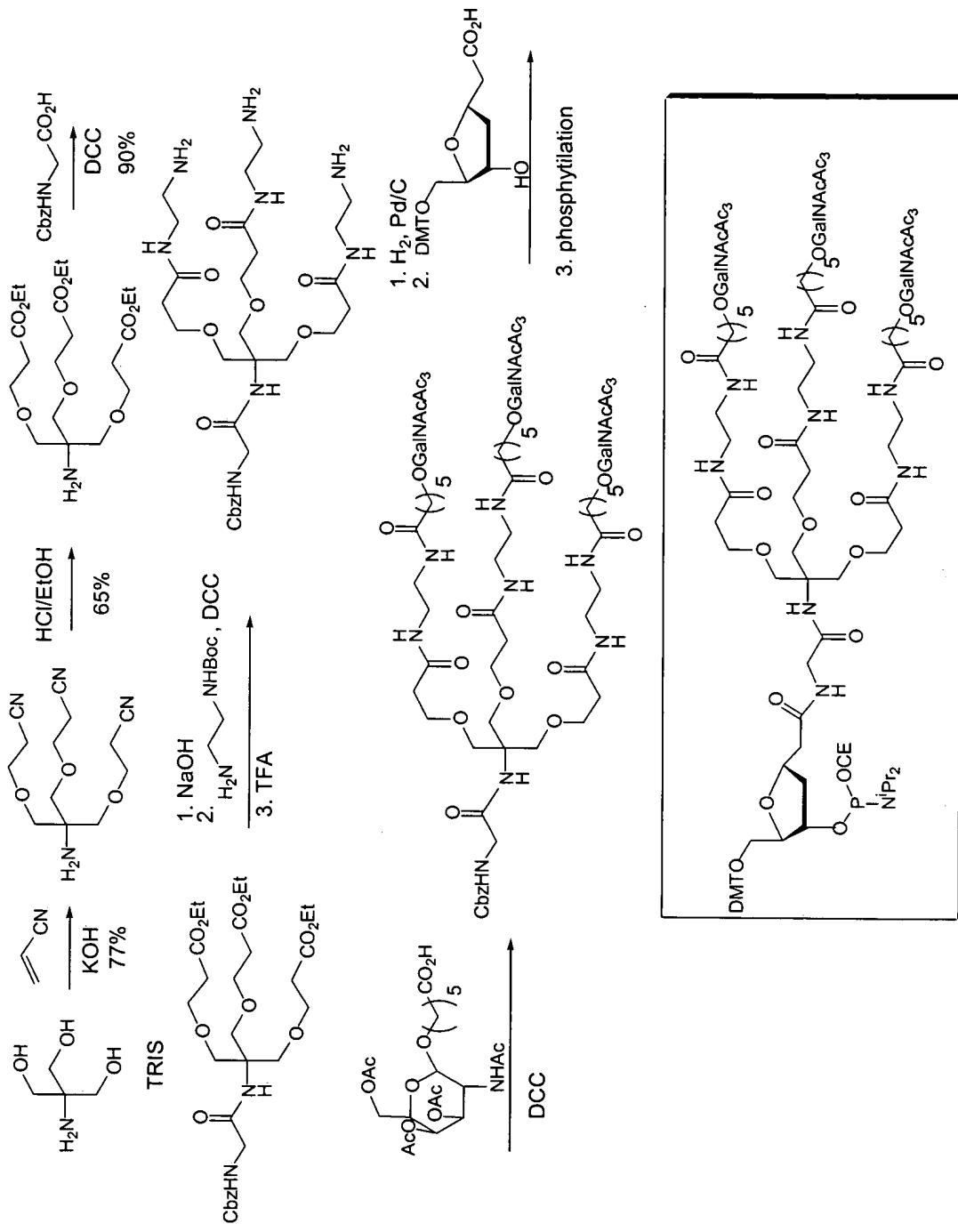


Figure 71: Synthesis of another Tri-Galactosamine Conjugate

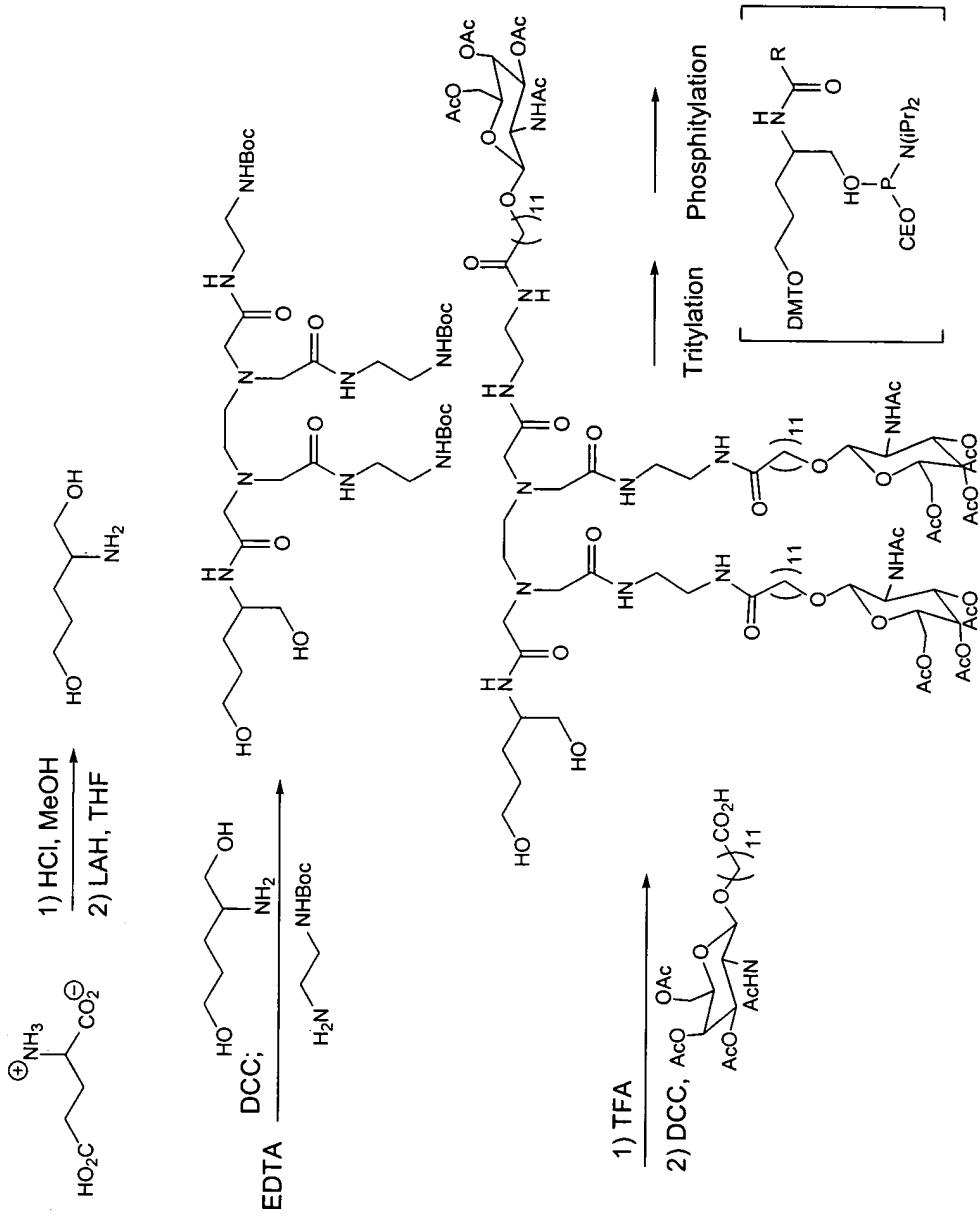


Figure 72: Alternate Synthesis of Tri-Galactosamine Conjugate

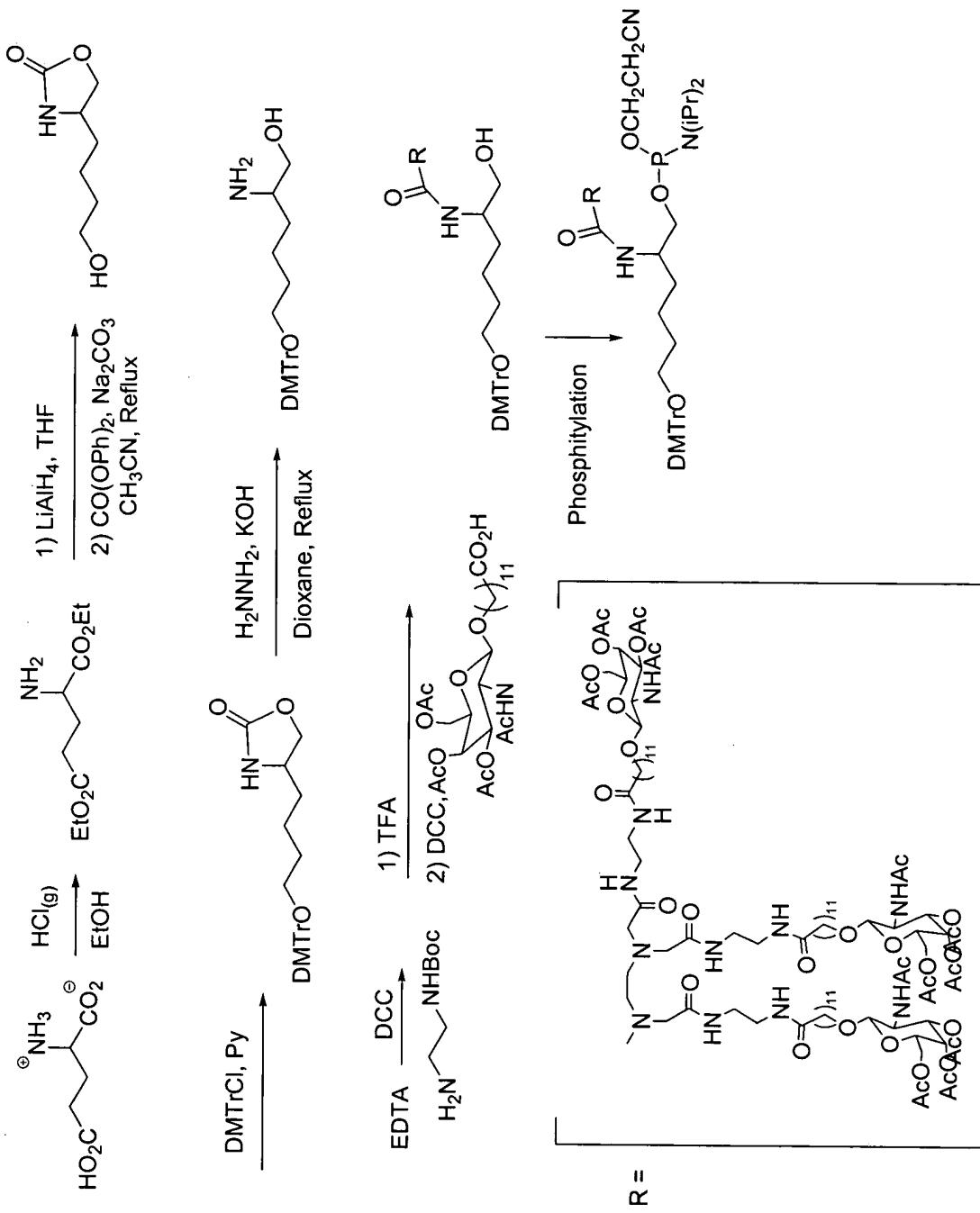


Figure 73: Synthesis of NHS Cholesterol Conjugate

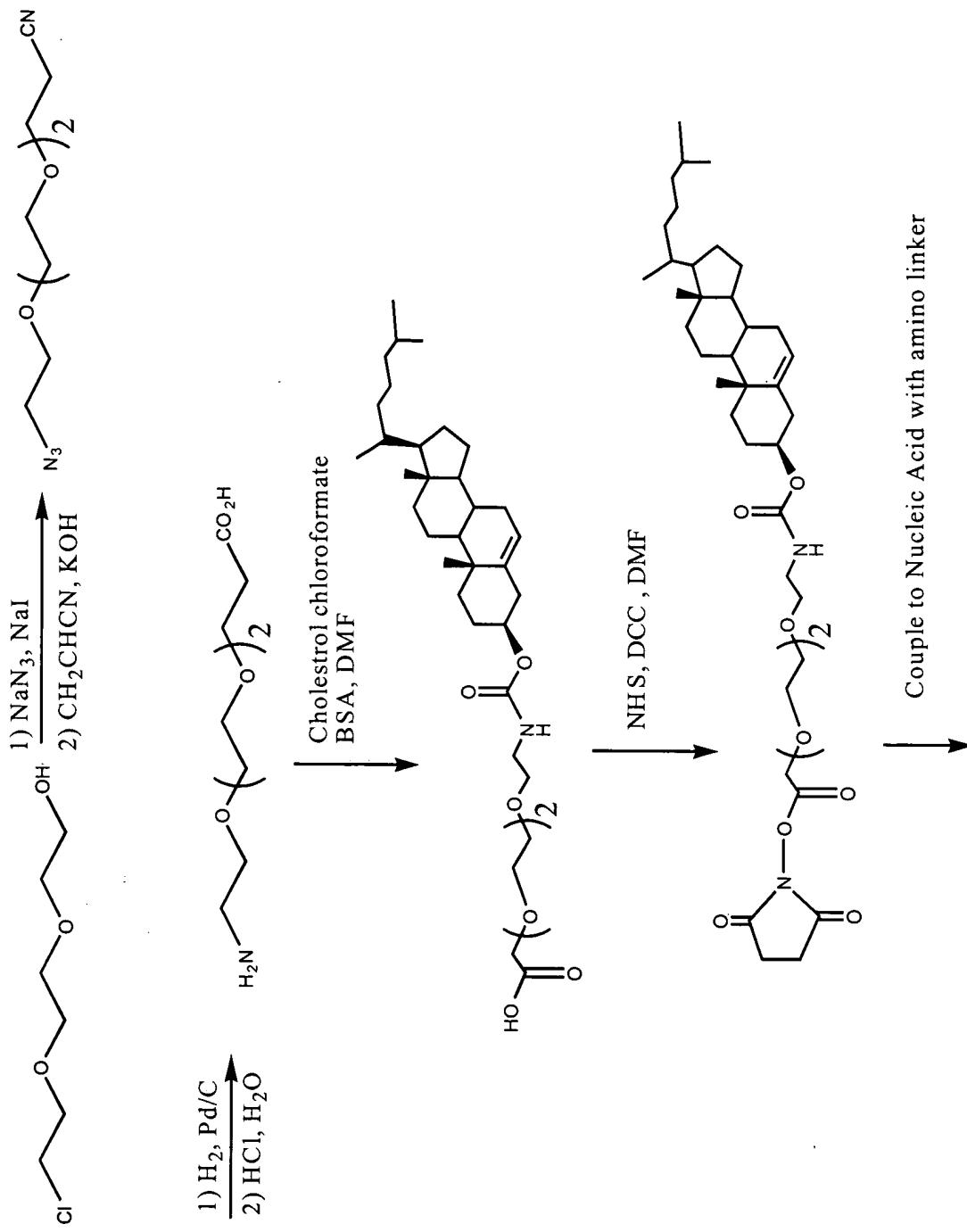


Figure 74: Phosphorylated siNA constructs

Asymmetric hairpin



Asymmetric duplex
siNA



Phosphates can be modified
as described herein



(n) = number of base
pairs (e.g. 3-18 bp)

Figure 75: 5'-phosphate modifications

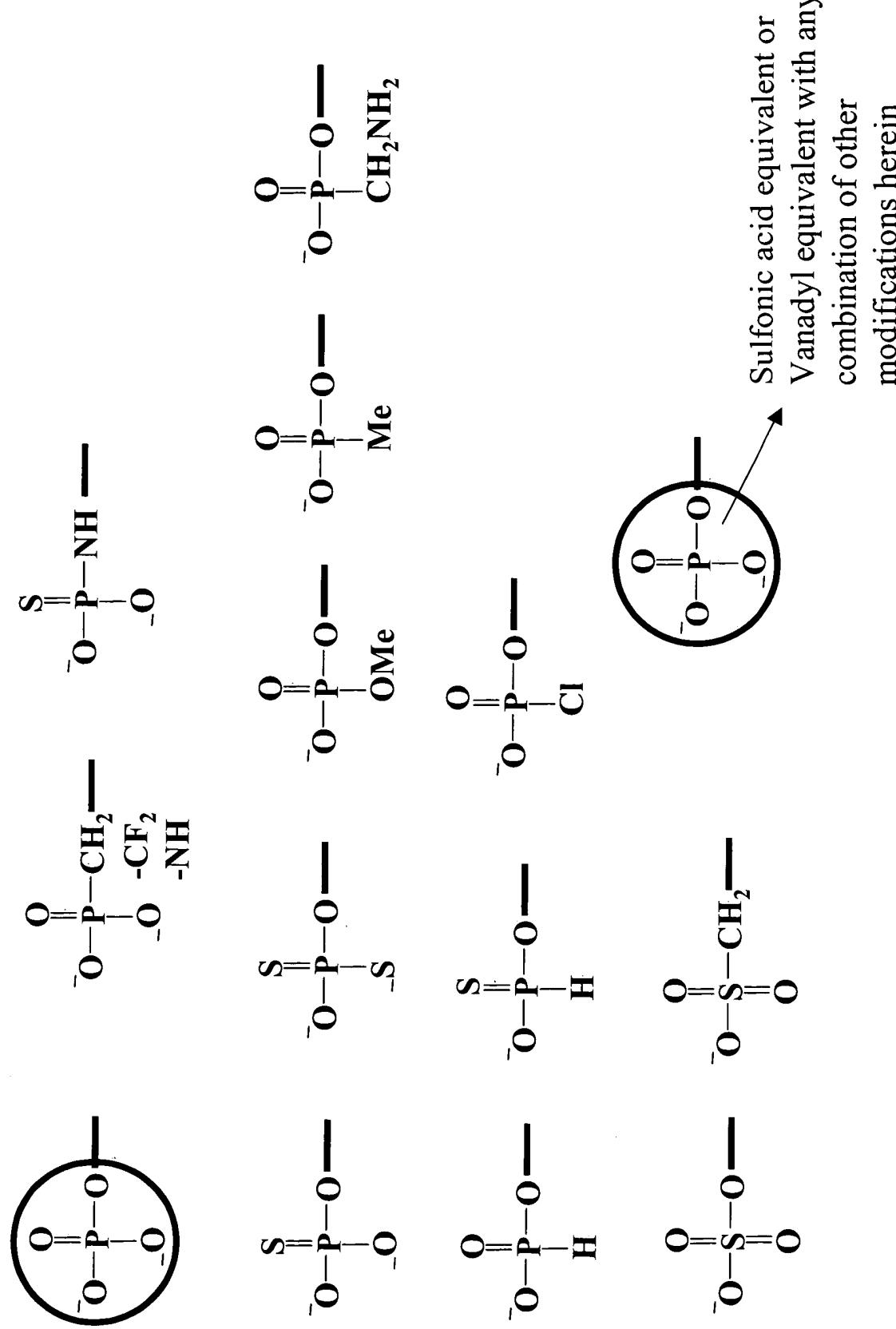


Figure 76: siNA Targeting VEGFR-1 Inhibits VEGF-Induced Rat Corneal Angiogenesis

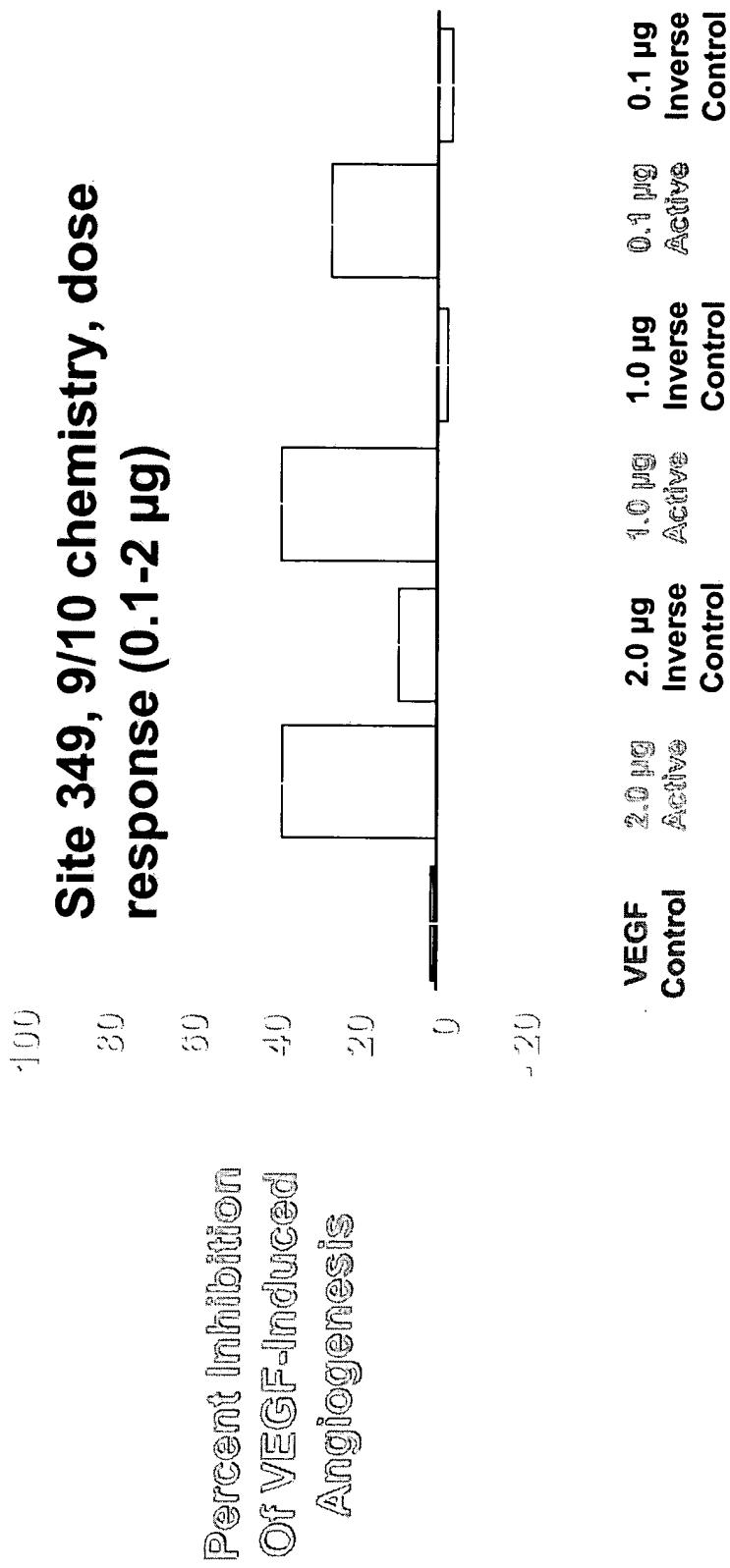


Figure 77: Duration of Effect of Modified siNA Constructs

HBV siRNA Duration: Day 3

A

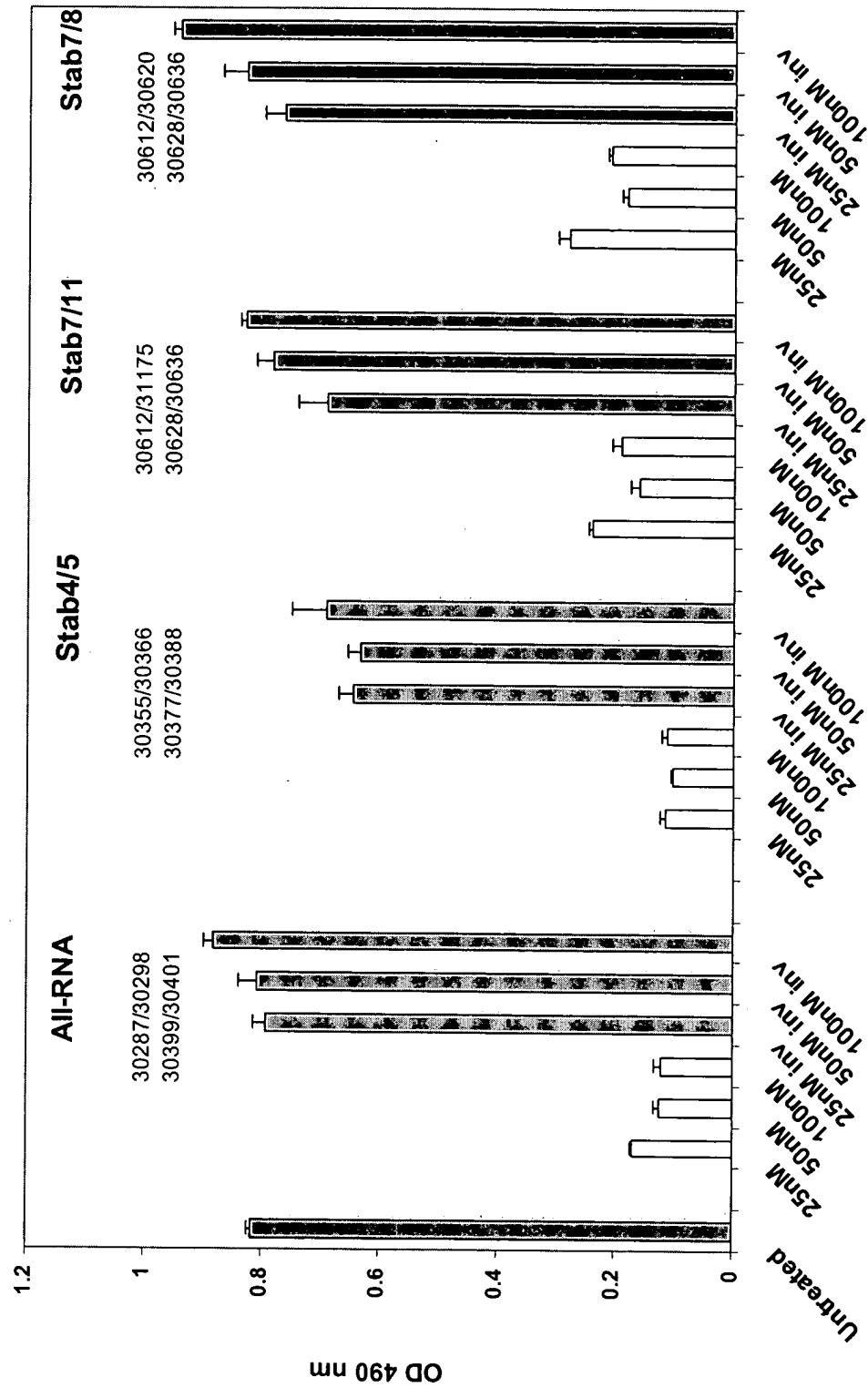


Figure 77: Duration of Effect of Modified siNA Constructs

HBV siRNA Duration: Day 9

B

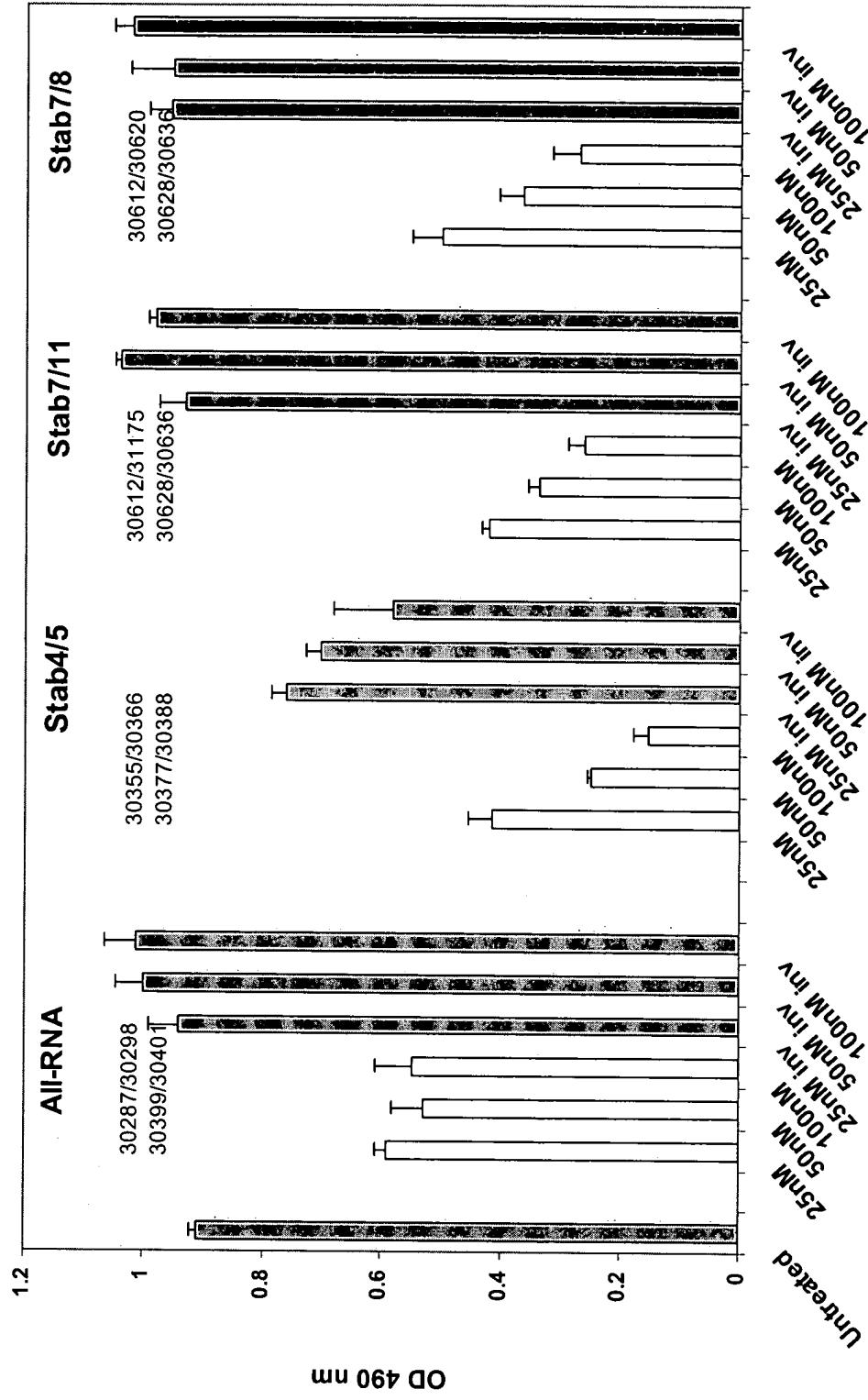


Figure 77: Duration of Effect of Modified siNA Constructs
HBV siRNA Duration: Day 21

C

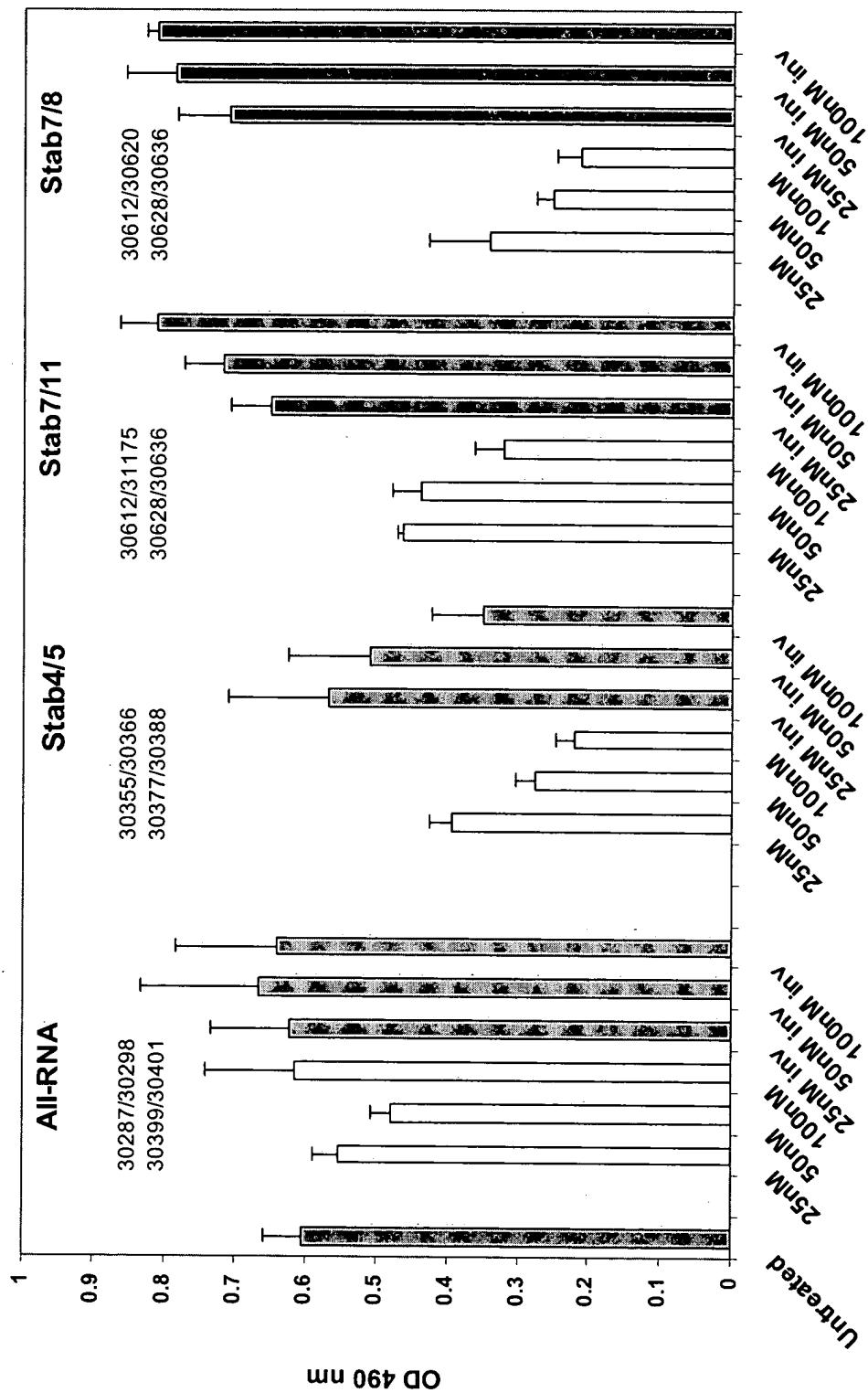


Figure 77: Duration of Effect of Modified siNA Constructs

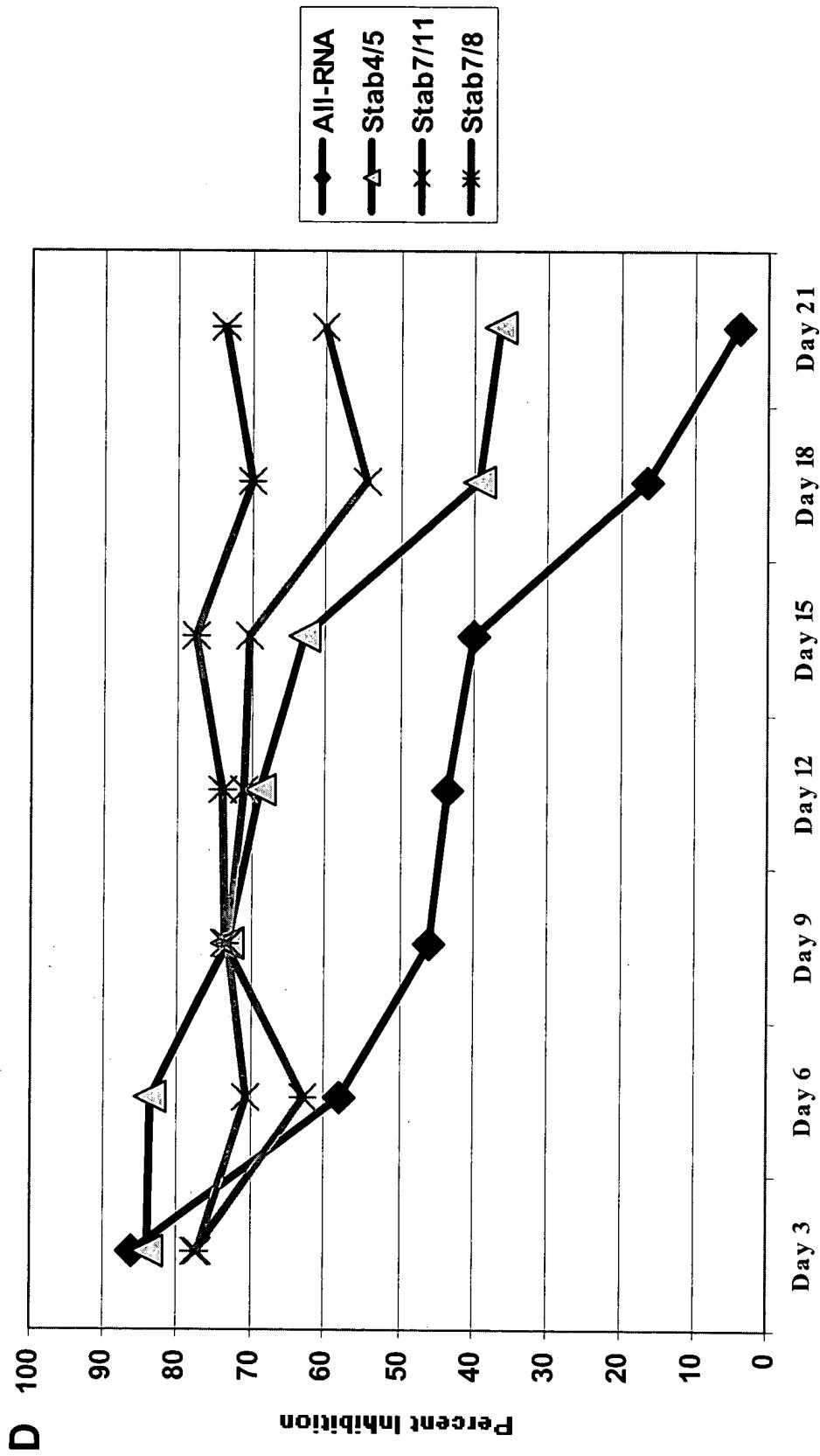


Figure 77: Duration of Effect of Modified siNA Constructs

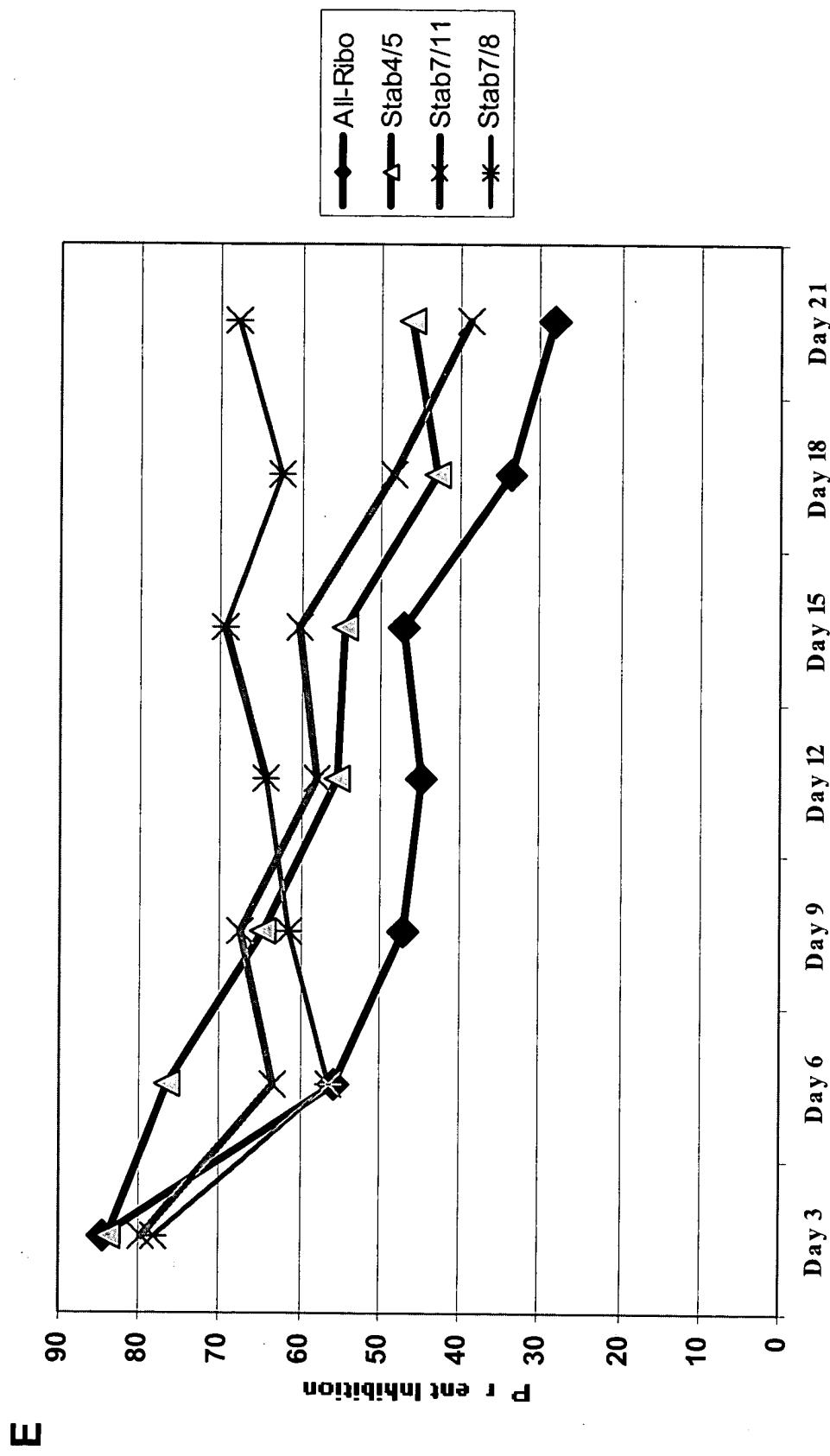


Figure 77: Duration of Effect of Modified siNA Constructs

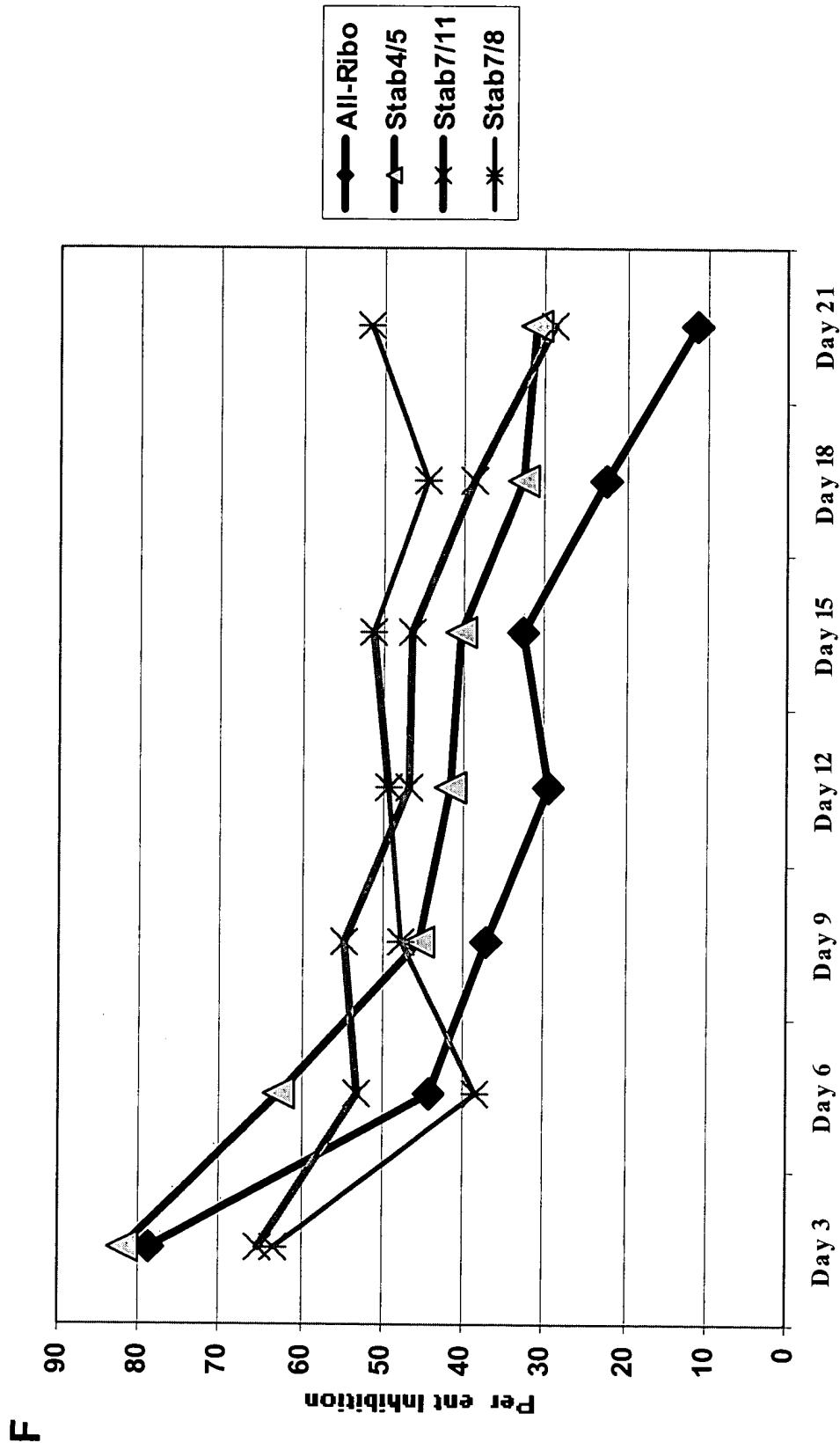


Figure 78: Phosphorylated siNA constructs

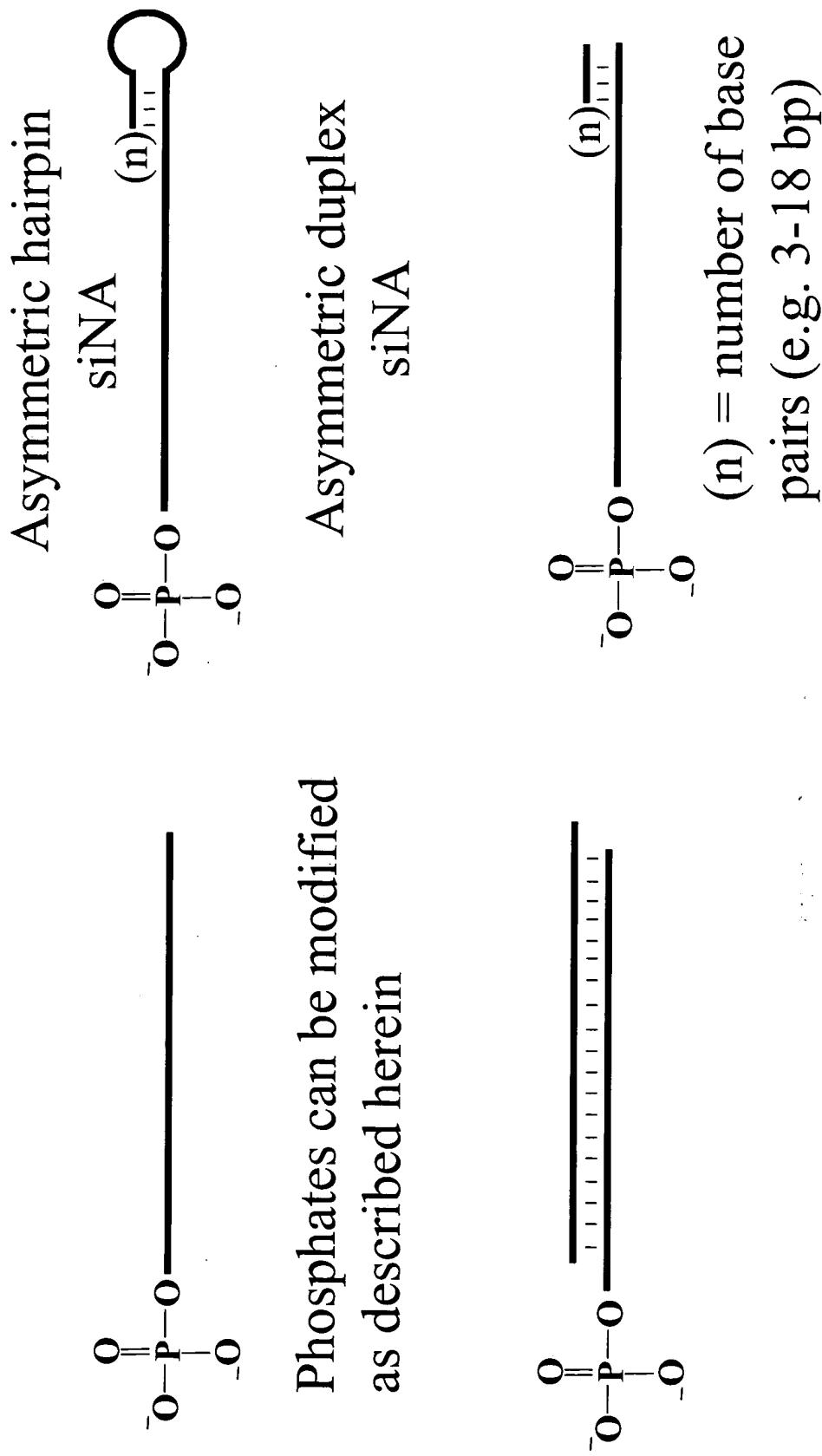
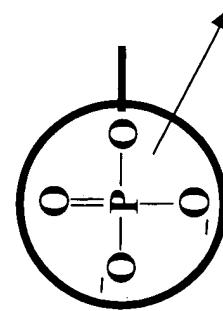
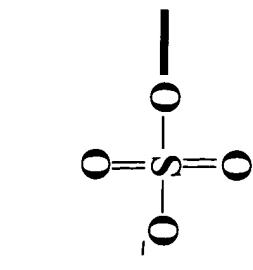
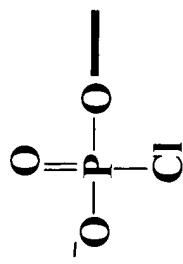
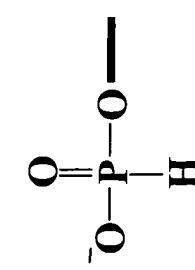
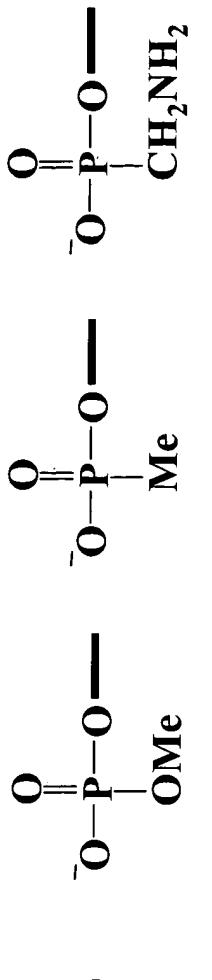
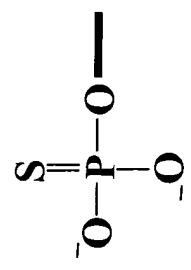
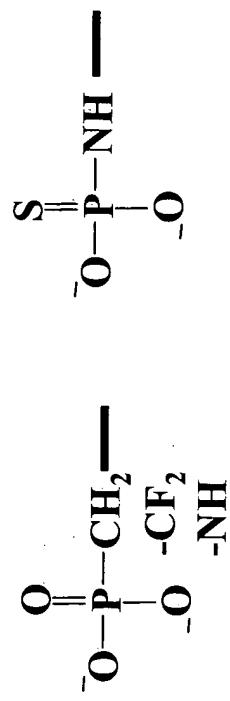
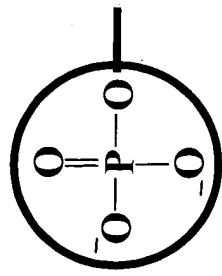


Figure 79: 5'-phosphate modifications



Sulfonic acid equivalent or
Vanadyl equivalent with any
combination of other
modifications herein

Figure 80: Serum HBV DNA in Mice Treated with siNA Via HDI

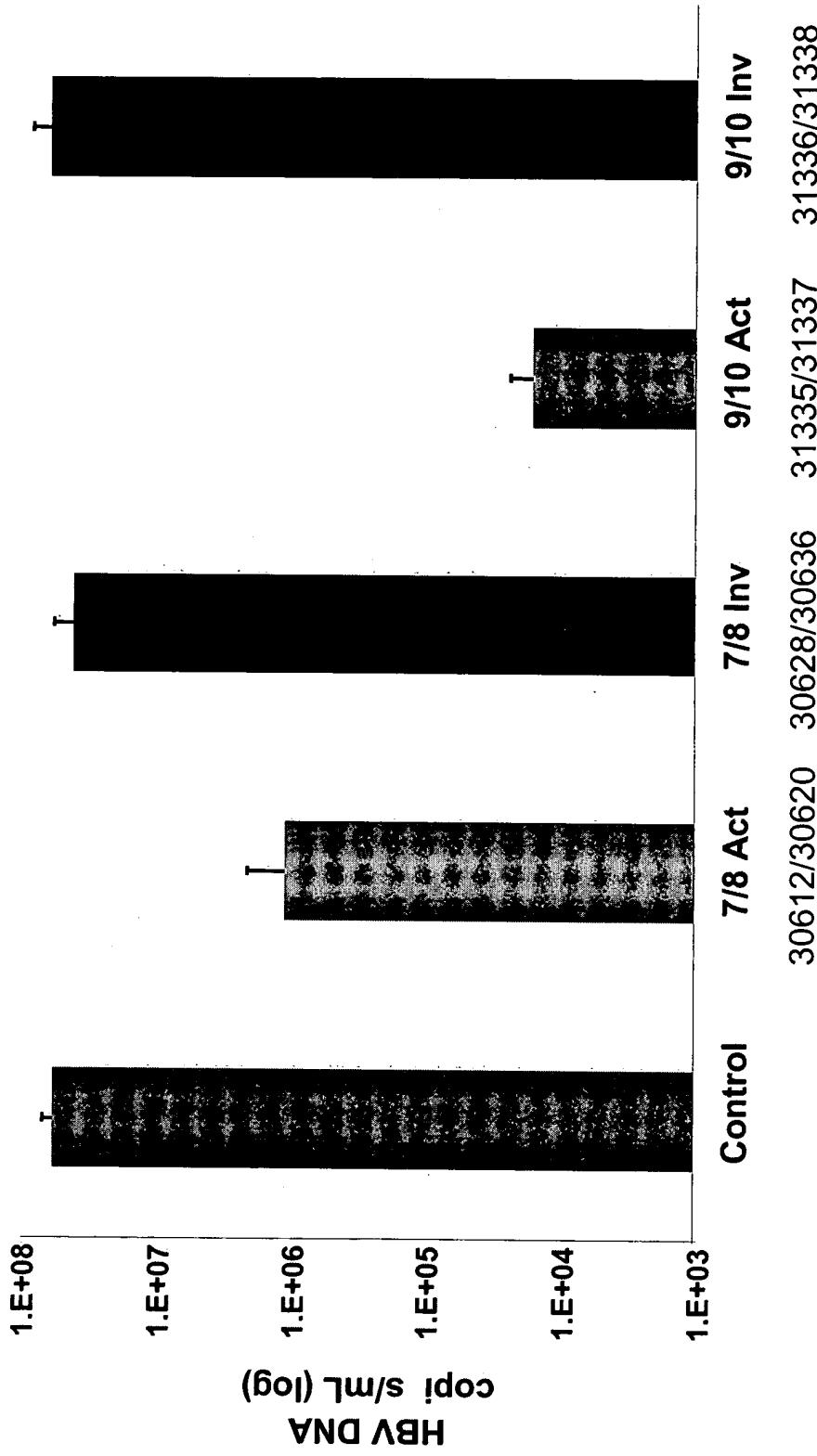


Figure 81: Serum HBsAg in Mice Treated with siNA Via HDI

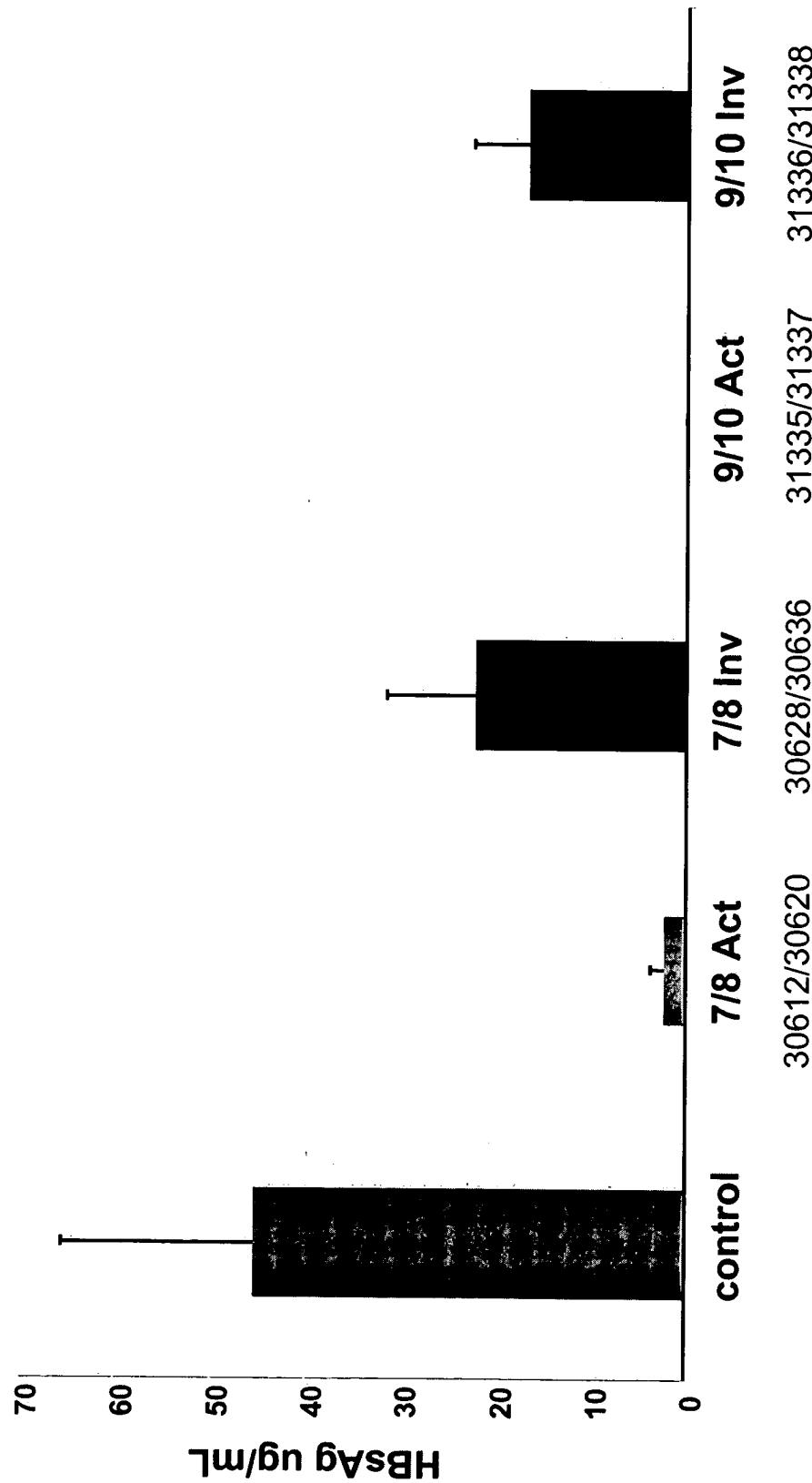


Figure 82: Liver HBV RNA in Mice Treated with siNA Via HDI

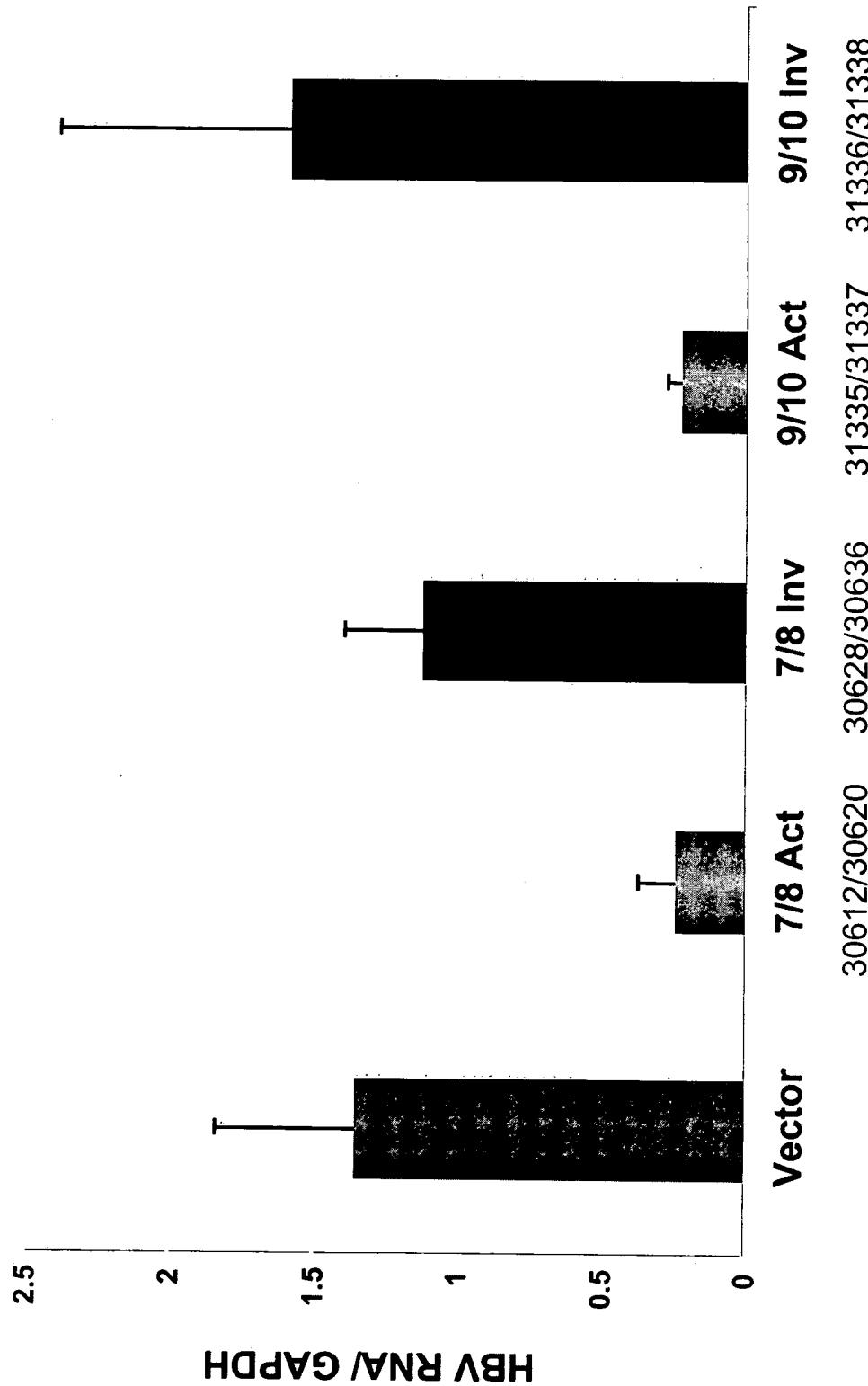
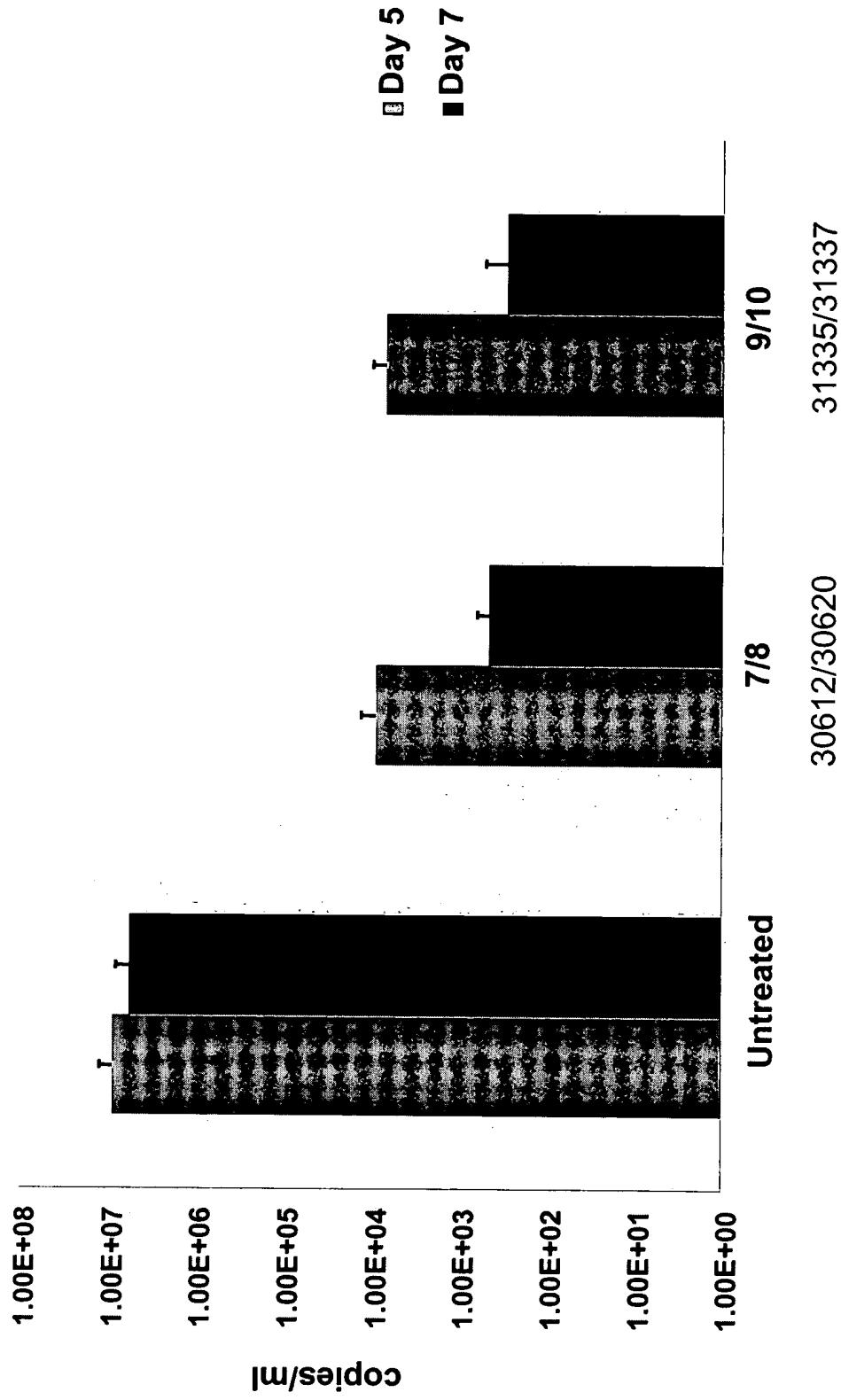
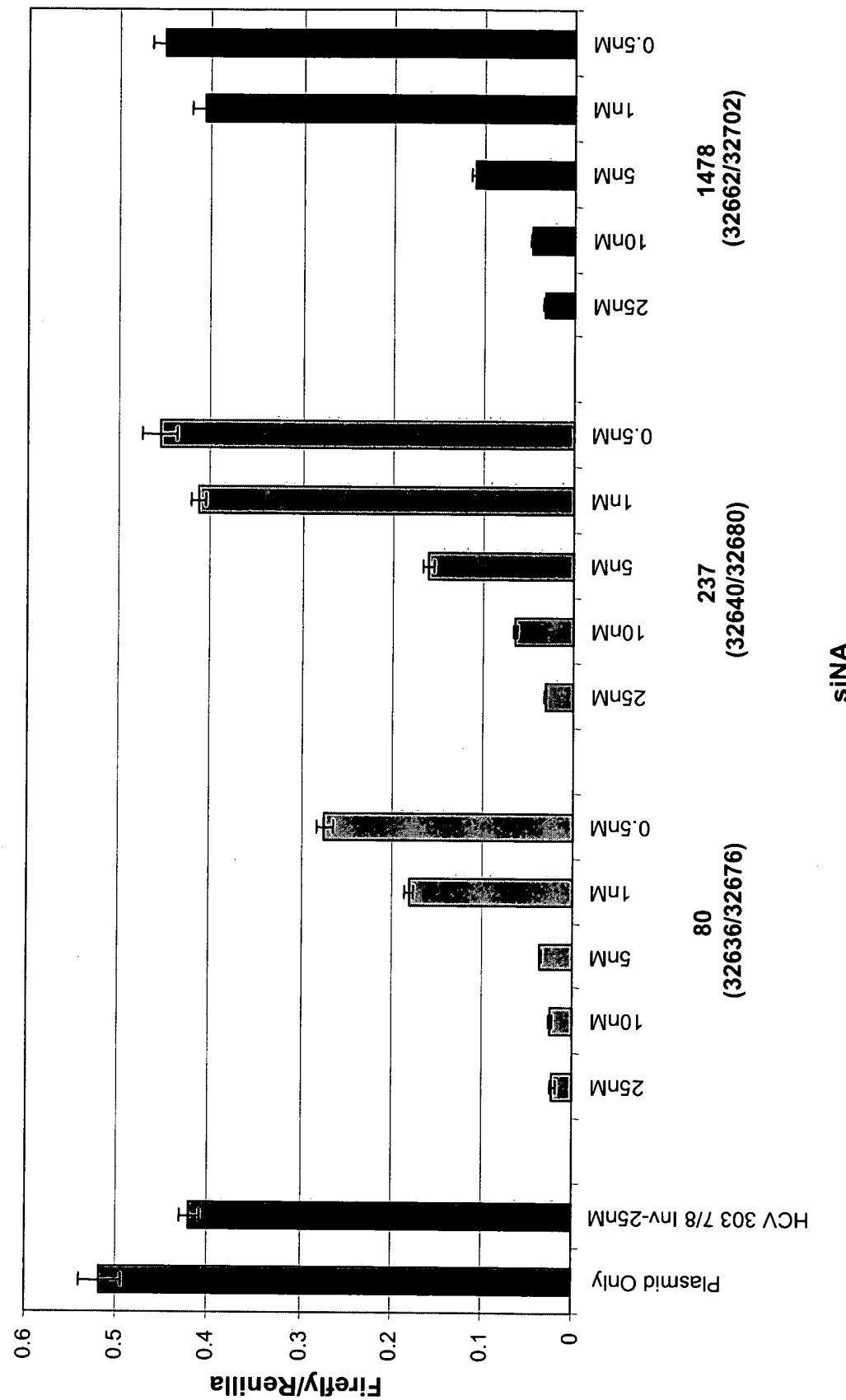


Figure 83: Serum HBV DNA in Mice Treated with siNA Via HDI 5 and 7 days post treatment



**Figure 84: Luciferase Dose Response
of select active siNA constructs**



**Figure 85: Luciferase Dose Response
of select active siNA constructs**

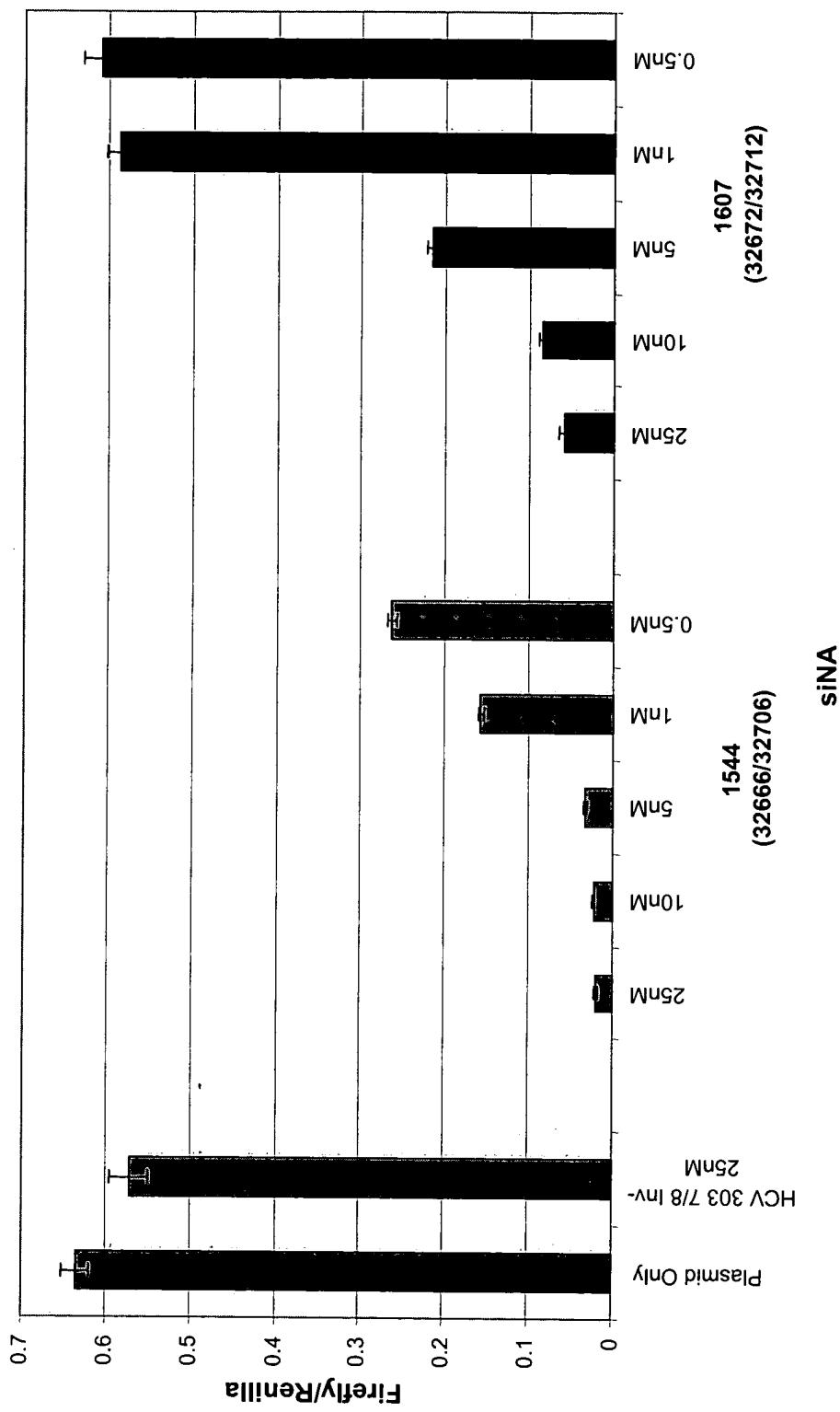


Figure 86: Activity of Stab 7/8 Stabilized siNAs in HCV Replicon

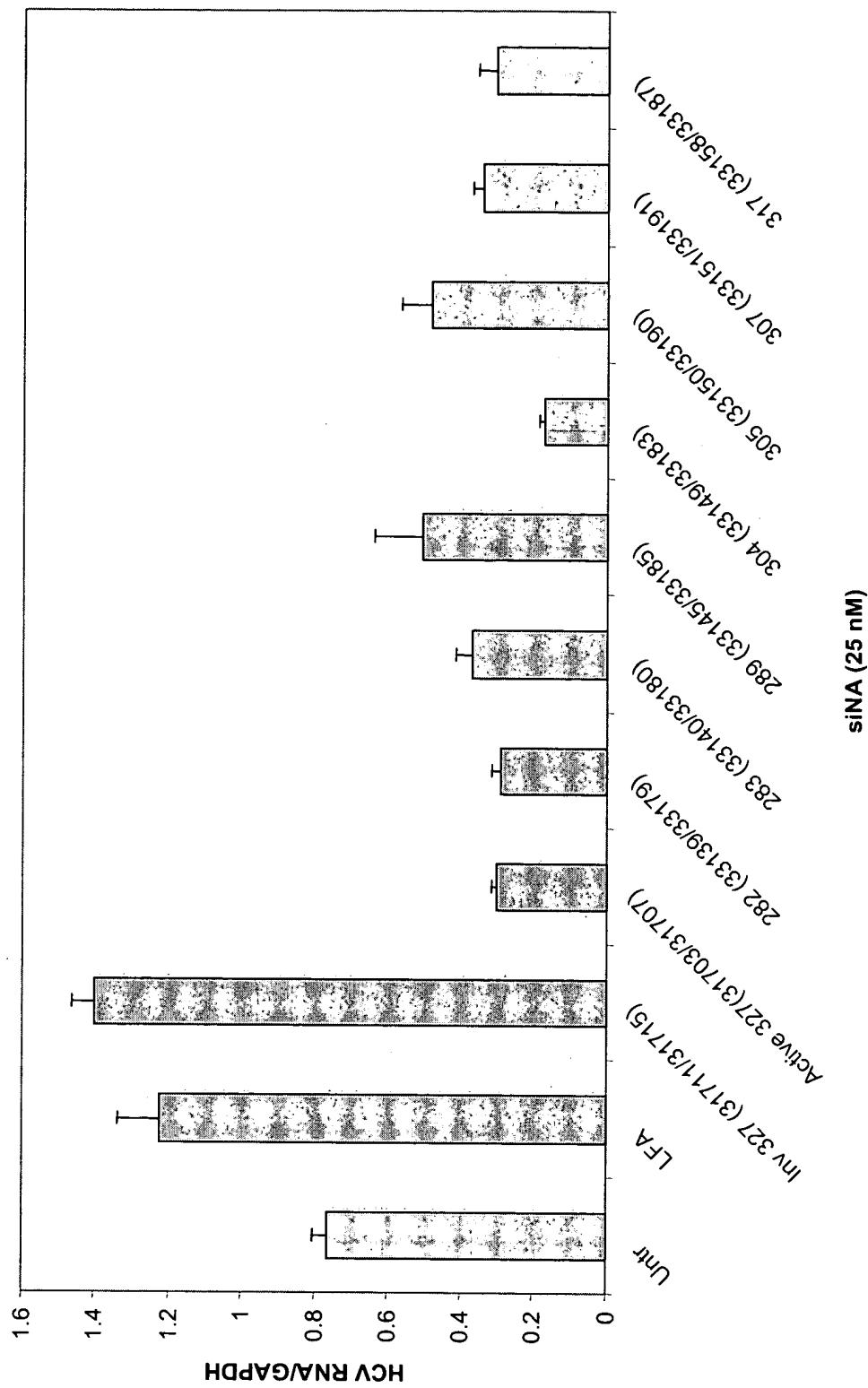


Figure 87: Activity of Stabilized 7/8 siNAs Against HBV in HepG2 Cells

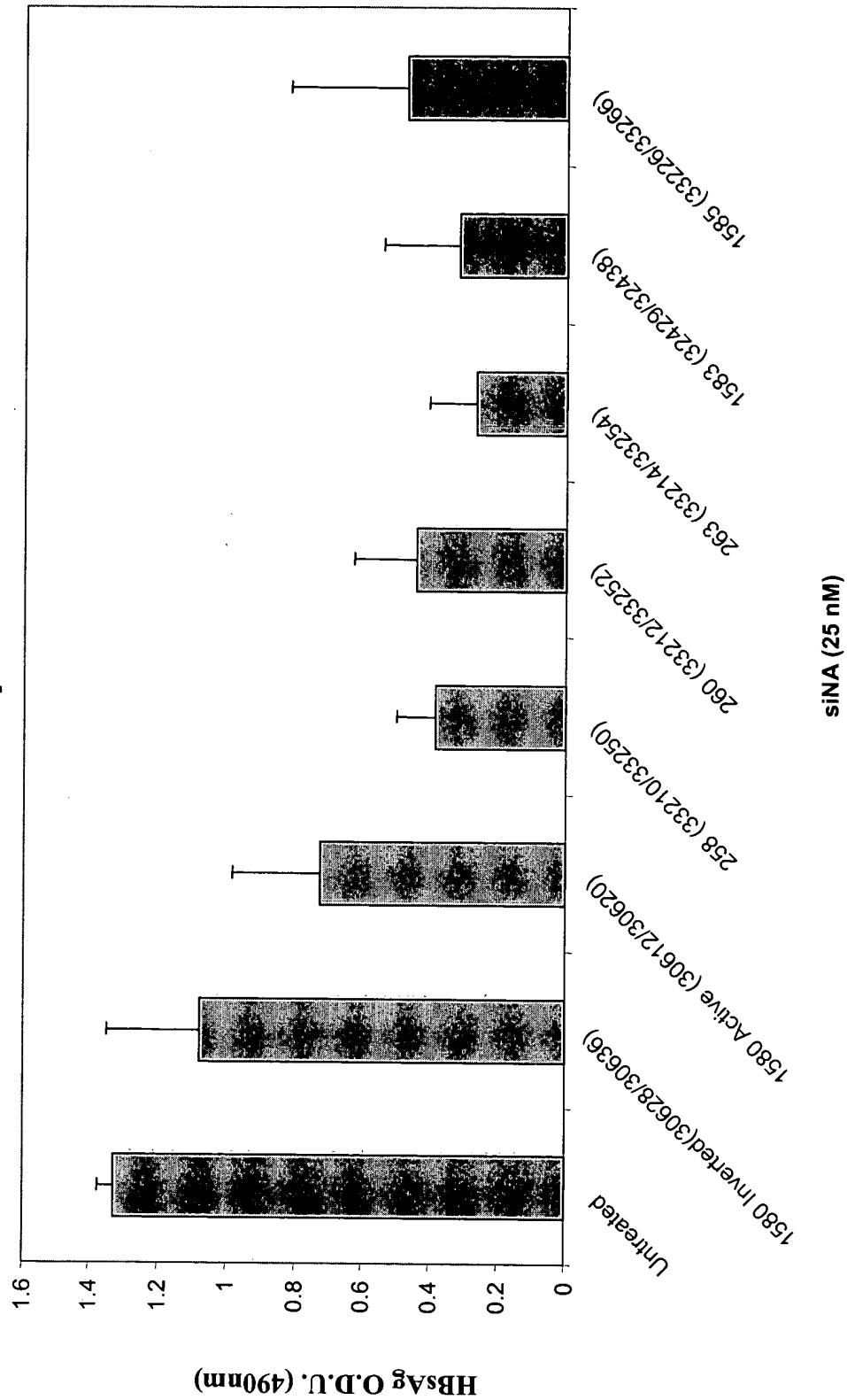


Figure 88: HBV/siNA to site 1580 Combination Constructs

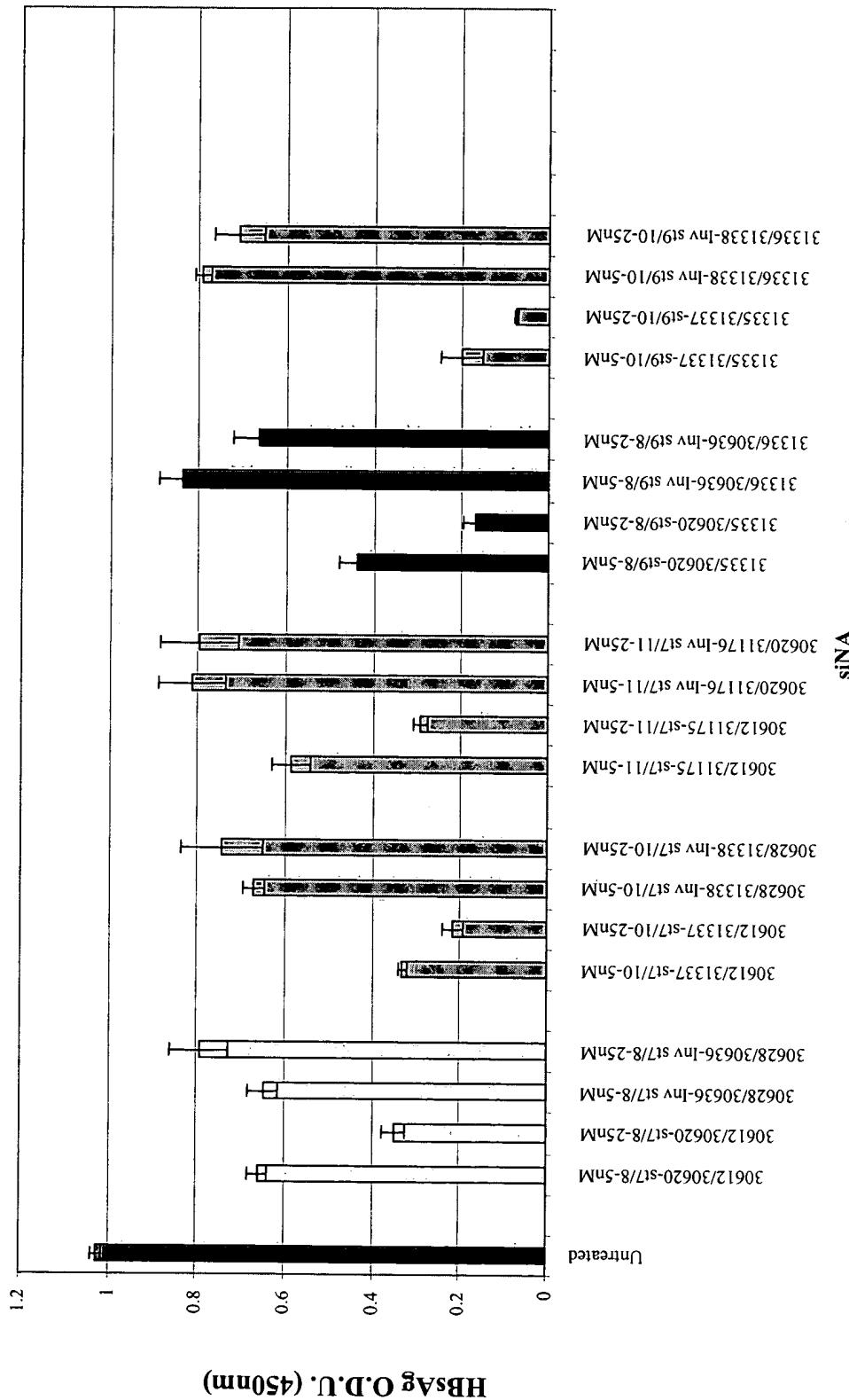


Figure 89: HBV/siNA to site 1580 Combination Constructs

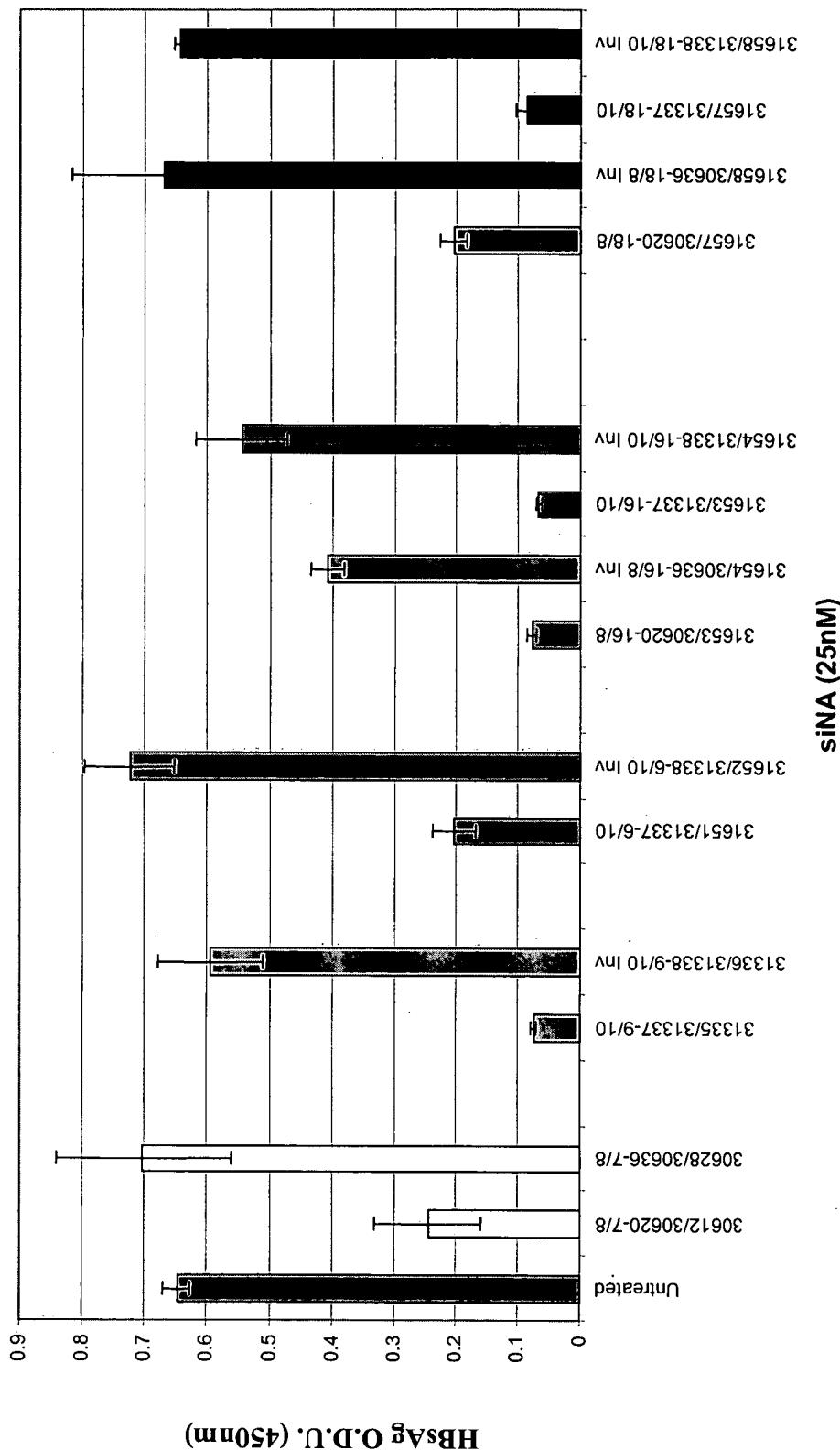


Figure 90: HBV/siNA to site 1580 Combination Constructs

